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(71) Applicants:
- **YAMANOUCHI PHARMACEUTICAL CO. LTD.**
  Tokyo 103-8411 (JP)
- **Rational Drug Design Laboratories**
  Tokyo 174-8612 (JP)

(72) Inventors:
- **KONTANI, Toru,**
  c/o Yamanouchi Pharma. Co., Ltd.
  Tsukuba-shi, Ibaraki 305-8585 (JP)
- **MIYATA, Junji,**
  c/o Yamanouchi Pharma. Co., Ltd.
  Tsukuba-shi, Ibaraki 305-8585 (JP)
- **HAMAGUCHI, Wataru,**
  c/o Yamanouchi Pharma. Co. Ltd.
  Tsukuba-shi, Ibaraki 305-8585 (JP)
- **MIYAZAKI, Yoji,**
  c/o Yamanouchi Pharma. Co., Ltd.
  Tsukuba-shi, Ibaraki 305-8585 (JP)
- **SUZUKI, Hiroshi,**
  c/o Yamanouchi Pharma. Co., Ltd.
  Tsukuba-shi, Ibaraki 305-8585 (JP)
- **NAKAI, Eiichi, c/o Yamanouchi Pharma. Co., Ltd.**
  Tsukuba-shi, Ibaraki 305-8585 (JP)
- **KAGEYAMA, Shunji,**
  c/o Yamanouchi Pharma. Co., Ltd.
  Tokyo 174-8612 (JP)

(74) Representative: **Bates, Philip Ian**
Reddie & Grose
16 Theobalds Road
London WC1X 8PL (GB)

(54) AMIDE DERIVATIVES

(57) The invention relates to a novel amide derivative which is an N-({[4-(substituted thiazol-4-yl)phenyl] carbamoyl}methyl)amide derivative having a characteristic in that an aryl or heteroaryl group as an aromatic ring group is directly substituted on the N atom of amido group. Since said amide derivative has excellent anti-herpesvirus action, it is useful as medicaments and antiviral agents, particularly as preventive or therapeutic agents for various diseases accompanied by *Herpesviridae* virus infections, illustratively, varicella (chickenpox) accompanied by varicella zoster virus infection, shingles accompanied by the recurrent infection of latent varicella zoster virus, labial herpes and herpes encephalitis accompanied by HSV-1 infection, genital herpes accompanied by HSV-2 and the like various herpesvirus infections.

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Description

Technical Field

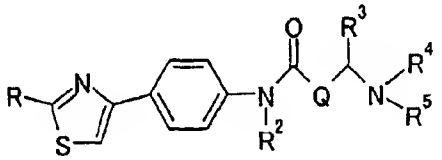
[0001] This invention relates to a novel amide derivative or a salt thereof useful as medicaments and antiviral agents, particularly for the prevention and treatment of diseases in which varicella zoster virus or the like herpesvirus is concerned.

Background of the Invention

[0002] Viruses belonging to the *Herpesviridae* family cause various infectious diseases in human and animals. For example, it is known that varicella zoster virus (VZV) causes varicella and shingles, and herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) cause herpes labialis, genital herpes and the like infections, respectively. In addition, infectious diseases caused by cytomegalovirus (CMV), EB virus (Epstein-Barr virus; EBV), human herpesviruses 6, 7 and 8 and the like herpesviruses have also been revealed in recent years.

[0003] Currently, acyclovir (ACV), its prodrugs varacyclovir (VCV) and fancyclovir (FCV) and the like nucleoside analogues are used as anti-herpesvirus drugs for VZV and HSV. These nucleoside analogues drugs are mono-phosphorylated into nucleoside monophosphate by viral thymidine kinase encoded by VZV and HSV and then converted into triphosphate compounds by cellular enzymes. Finally, the tri-phosphorylated nucleoside analogues are incorporated during the replication of viral genomic DNA by herpesvirus DNA polymerase and inhibit elongation reaction of viral DNA chains. Thus, since the reaction mechanism of existing anti-herpesvirus agents is based on the "competitive inhibition" for deoxynucleoside triphosphate, it is necessary to use these drugs in a high concentration in order to exert their antiviral effects. Actually, it is the present situation that these anti-herpes nucleoside analogues are administered in a high dosage of from several hundred mg to several g as their clinical dose. In addition, since nucleoside analogues are able to incorporate into host genomic DNA by DNA polymerase of the host, there is some apprehension about their mutagenicity.

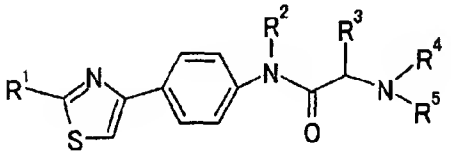
[0004] On the other hand, some drugs which are non-nucleoside analogues and show anti-herpesvirus activity have recently been reported. For example, WO 97/24234 discloses amide or sulfonamide derivatives represented by the following formula (G) wherein an N atom is substituted with thiazolylphenylcarbamoylmethyl group or the like, which shows anti-HSV-1 activity and anti-CMV activity by inhibiting an HSV helicase-primase enzyme complex. However, the anti-VZV activity of these compounds is not illustratively disclosed.



(G)

(In the formula, R is hydrogen, lower alkyl, amino, lower alkylamino or the like, R^2 is hydrogen or lower alkyl, Q is not present or methylene, R^3 is hydrogen, lower alkyl or the like, R^4 is unsubstituted or substituted phenyl(lower) alkyl, 1-indanyl, 2-indanyl, (lower cycloalkyl)-(lower alkyl), (Het)-(lower alkyl) or the like, R^5 is phenylsulfonyl, 1- or 2-naphthylsulfonyl, (Het)-sulfonyl, (unsubstituted or substituted phenyl)-Y-(CH_2)nC(O), (Het)-(CH_2)nC(O) or the like, Y is O or S, and n is 0, 1 or 2. See said document for details.)

[0005] WO 00/29399 also discloses amide or sulfonamide derivatives represented by the following formula (H) wherein an N atom is substituted with thiazolylphenylcarbamoylmethyl group, which shows anti-HSV-1 activity and anti-CMV activity, but the anti-VZV activity of these compounds is not illustratively disclosed.



(H)

(In the formula, R^1 is NH_2, R^2 is H, R^3 is H, R^4 is CH_2Ph, CH_2-(4-pyridyl), CH_2-cyclohexyl or the like, and R^5 is CO-(substituted phenyl), CO-(unsubstituted or substituted hetero ring) or the like. See said document for details.)

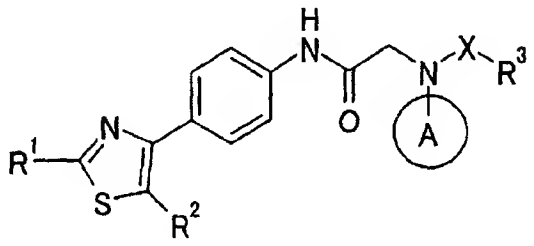
[0006] In addition, recently, there are reports on various herpesvirus protease inhibitors (Waxman Lloid *et al.*, 2000, *Antiviral Chemistry and Chemotherapy,* 11, 1 - 22) and N-(carbonylphenyl)benzamide derivatives as HSV primase inhibitors (WO 00/58270). However, these documents do not disclose compounds having good anti-VZV activity, too.

[0007] Development of a non-nucleoside analogue anti-herpesvirus agent having sufficient anti-VZV activity and also having high safety is in great demand.

Disclosure of the Invention

[0008] As a result of intensive studies on compounds having anti-varicella zoster virus (anti-VZV) activity, the present inventors have accomplished the invention by finding that novel amide derivatives (including sulfonamide derivatives) characterized in that, as shown in the following general formula (I), an aryl group or heteroaryl group as an aromatic ring group is directly, without mediating alkylene chain, substituted as the group A on an amido group in which the N atom is substituted with thiazolylphenylcarbamoylmethyl group have excellent anti-VZV activity.

[0009] That is, the invention relates to a novel amide derivative represented by the following general formula (I) or a salt thereof.



(I)

(Symbols in the formula have the following meanings;

R^1 and R^2: the same or different from each other, and each represents -H, -lower alkyl, -lower alkenyl, -lower alkynyl, -cycloalkyl, -cycloalkenyl, -NRaRb, -NRc-NRaRb, -NRc-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -NRc-C(=NH)-NRaRb, -(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -lower alkylene-NRaRb, -lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -NRaCORb, -NRaCO-ORb, -NRaCO-NRbRc, -NRaCO-lower alkylene-NRbRc, -NRaCO-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -$NRaSO_2$Rb, -$NRaSO_2$-NRbRc, -$NRaSO_2$-lower alkylene-NRbRc, -$NRaSO_2$-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -CONRaRb, -SO_2NRaRb, -COORa, -SO_2Ra, -CONRa-ORb, -OCORa, -ORa, -halogen, -CORa, -NO_2, -CN or -halogeno lower alkyl,

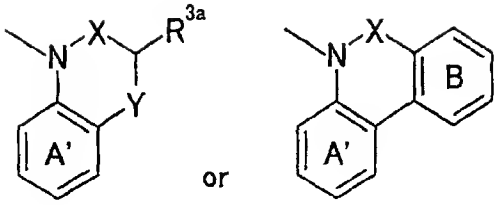
Ra, Rb and Rc: the same or different from one another, and each represents -H, -lower alkyl, -lower alkenyl, -lower alkynyl, -cycloalkyl, -cycloalkenyl, -aryl, -5- or 6-membered monocyclic heteroaryl or -lower alkylene-aryl,

A: -aryl which may have one or more substituents, -heteroaryl which may have one or more substituents, -saturated carbon ring-condensed aryl which may have one or more substituents or -saturated heterocyclic ring-condensed aryl which may have one or more substituents, wherein the saturated carbon ring-condensed aryl and saturated heterocyclic ring-condensed aryl bind to the adjacent N atom via C atom of the aromatic ring,

X: CO or SO_2,

R^3: -alkyl which may have one or more substituents, -alkenyl which may have one or more substituents, -alkynyl which may have one or more substituents, -cycloalkyl which may have one or more substituents, -cycloalkenyl which may have one or more substituents, -aryl which may have one or more substituents, -hetero ring which may have one or more substituents or

-NRaRb, or it may form a group represented by the following formula together with the adjacent group -N(A)-X-,



Y: O, S, a bond or CH_2,
R^{3a}: -H, -cycloalkyl which may have one or more substituents,
-cycloalkenyl which may have one or more substituents,-aryl which may have one or more substituents or -hetero ring which may have one or more substituents, and
A' and B: the same or different from each other, and each represents benzene ring which may have one or more substituents. The same shall apply hereinafter.)

[0010] In addition, the invention relates to a pharmaceutical composition which contains the amide derivative represented by the aforementioned general formula (I) or a salt thereof and a pharmaceutically acceptable carrier, and an anti-herpesvirus agent, particularly an anti-VZV agent.

[0011] The compounds of general formula (I) are further described.

[0012] In this specification, the term "lower" means a straight or branched hydrocarbon chain having from 1 to 6 carbon atoms. As the "lower alkyl", it is preferably an alkyl group having from 1 to 4 carbon atoms, particularly preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl group. As the "lower alkenyl", it is preferably an alkenyl group having from 2 to 5 carbon atoms, particularly preferably vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl or 3-butenyl group. As the "lower alkynyl", it is preferably an alkynyl group having from 2 to 5 carbon atoms, particularly preferably ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl or 1-methyl-2-propynyl group. Also, as the "lower alkylene", it is preferably an alkylene group having from 1 to 3 carbon atoms, particularly preferably methylene, ethylene, trimethylene or dimethylmethylene group.

[0013] As the "alkyl", it is preferably a straight or branched chain alkyl group having from 1 to 10 carbon atoms, and its further preferred examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 2,2-diethylpropyl, n-octyl and n-decyl groups. As the "alkenyl" and "alkynyl", they are preferably straight or branched chain groups having from 2 to 10 carbon atoms.

[0014] As the "aryl", it means an aromatic hydrocarbon ring group and is preferably an aryl group having from 6 to 14 carbon atoms, and phenyl and naphthyl groups are desirable. As the "cycloalkyl", it is a cycloalkyl group having from 3 to 10 carbon atoms, which may have a cross-link, and preferred are cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl groups. As the "cycloalkenyl", it is preferably a cycloalkenyl group having from 3 to 10 carbon atoms, and particularly preferred are cyclopentenyl and cyclohexenyl groups. The "saturated carbon ring-condensed aryl" is a condensed ring group in which benzene ring or naphthalene ring is condensed with a C_{5-6} saturated carbon ring, and preferred are indanyl and tetrahydronaphthyl.

[0015] The "hetero ring" is a saturated or unsaturated monocyclic or bicyclic or tricyclic 5- to 8-membered hetero ring containing from 1 to 4 hetero atoms selected from N, S and O. Preferred are "heteroaryl", "5- to 8-membered saturated heterocyclic ring" and "saturated heterocyclic ring-condensed aryl" which are described in the following.

[0016] The "5- or 6-membered monocyclic heteroaryl" is a 5-or 6-membered monocyclic heteroaryl containing from 1 to 4 hetero atoms selected from N, S and O, and preferred are furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl and triazinyl. The "heteroaryl" includes the aforementioned 5- or 6-membered monocyclic heteroaryl and a bi- or tricyclic heteroaryl condensed with benzene ring or in which heteroaryl rings are condensed with each other. In this connection, preferred as the monocyclic heteroaryl are those described in the foregoing, and preferred as the bi- or tri-cyclic heteroaryl include benzofuranyl, benzothienyl, benzothiadiazolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzoimidazolyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, benzodioxolyl, imidazopyridyl, indolidinyl, carbazolyl, dibenzofuranyl and dibenzothienyl groups.

[0017] The "5- to 8-membered monocyclic saturated heterocyclic ring" is a 5- to 8-membered monocyclic saturated heterocyclic ring which contains from 1 to 4 hetero atoms selected from N, S and O and may have a cross-link, and preferred are tetrahydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, thiepanyl, thiocanyl, pyrrodinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, azepanyl, diazepanyl, piperidinyl and morpholinyl groups. Further preferred are 5- to 7-membered ring groups. In addition, the "nitrogen-containing saturated heterocyclic ring" is a group having at least one ring nitrogen

atom among the aforementioned "5- to 8-membered monocyclic saturated heterocyclic ring", and its preferred examples include piperidino, morpholino, 1-piperazinyl and 1-pyrolidinyl.

[0018] The "saturated heterocyclic ring-condensed aryl" is the aforementioned 5- to 8-membered monocyclic saturated heterocyclic ring to which benzene ring or naphthalene ring is condensed, and preferred are 3,4-dihydro-2H-1,4-benzoxadinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxynyl, chromanyl, isochromanyl, 3,4-dihydro-2H-1-benzothiopyranyl, 3,4-dihydro-1H-2-benzothiopyranyl, indolinyl, isoindolinyl, 1,2,3,4-tetrahydroquinolyl and 1,2,3,4-tetrahydroisoquinolyl groups.

[0019] When the ring A is a "saturated carbon ring-condensed aryl" or a "saturated heterocyclic ring-condensed aryl", the ring A binds to the N atom of adjacent amido group via C atom of the aromatic ring. On the other hand, when R^3 is a "saturated carbon ring-condensed aryl" or a "saturated heterocyclic ring-condensed aryl", the R^3 binds to the adjacent group X via C atom of the aromatic ring or the C atom or N atom of the saturated ring.

[0020] As the "halogen", F, Cl, Br and I atoms can be exemplified. The "halogeno lower alkyl" is the aforementioned lower alkyl on which one or more of the above halogen are substituted, and is preferably $-CF_3$.

[0021] The substituents in the "alkyl which may have one or more substituents", "alkenyl group which may have one or more substituents" and "alkynyl group which may have one or more substituents" are preferably 1 to 4 substituents selected from the following group C.

[0022] Group C: -cycloalkyl, -cycloalkenyl, -aryl, -NRaRb, -NRc-NRaRb, -(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl, -lower alkylene-COORa and -NRaRb), -NRc-(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl, -lower alkylene-COORa and -NRaRb), -O-lower alkylene-NRaRb, -O-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl, -lower alkylene-COORa and -NRaRb), -O-lower alkylene-ORa, -O-lower alkyl-COORa,
-COORa, -halogen, -CORa, $-NO_2$, -CN, -ORa, -O-(halogeno lower alkyl, -SRa, -SORa, $-SO_2Ra$, -CO-NRaRb, -CO-(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl, -lower alkylene-COORa and -NRaRb), -NRa-CORb, $-SO_2NRaRb$ and =O (oxo) (wherein Ra, Rb and Rc are as described in the above).

[0023] The substituents in "the cycloalkyl which may have one or more substituents", "cycloalkenyl which may have one or more substituents", "aryl which may have one or more substituents", "saturated carbon ring-condensed aryl which may have one or more substituents", "saturated heterocyclic ring-condensed aryl which may have one or more substituents", "5- to 8-membered hetero ring which may have one or more substituents" and "benzene ring which may have one or more substituents" are preferably 1 to 5 substituents selected from the following group D.

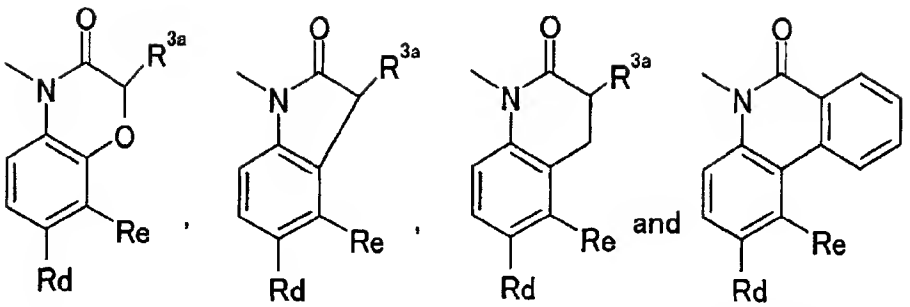
[0024] Group D: -(lower alkyl which may have one or more substituents selected from -ORa, -SRa, -CN, -COORa, -CONRa, -NRaRb and -(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl, -lower alkylene-COORa and -NRaRb)), -lower alkenyl, -lower alkynyl, -halogeno lower alkyl, 5- or 6-membered monocyclic heteroaryl and the substituents described in the above group C.

[0025] Further preferred are 1 to 4 substituents selected from the following group D1.

[0026] Group D1: -lower alkyl, -phenyl, -halogeno lower alkyl, -COOH, -COO-lower alkyl, -halogen, $-NO_2$, -CN, -OH, -O-lower alkyl, -O-halogeno lower alkyl, -O-lower alkylene-O-lower alkyl, -O-lower alkylene-COOH, -O-lower alkylene-COO-lower alkyl, -O-lower alkylene-NH_2, -O-lower alkylene-NH-lower alkyl, -O-lower alkylene-N(lower alkyl)$_2$, -O-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), NH_2, -NH-lower alkyl, -N(lower alkyl)$_2$, -(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl and -lower alkylene-COORa), -NHCO-lower alkyl, -N(lower alkyl)CO-lower alkyl, $-CONH_2$, -CONH-lower alkyl, -CON(lower alkyl)$_2$, =O(oxo), -SH, -S-lower alkyl, -SO-lower alkyl and $-SO_2$-lower alkyl groups.

[0027] A compound including S atom-containing saturated heterocyclic ring may form an oxide (SO) or dioxide (SO_2) compound by substitution of 1 or 2 =O(oxo) on said S atom.

[0028] As the group formed from R_3 together with the adjacent group -N(A)-X-, the following groups can be preferably cited.



(In the formula, R^{3a} is -H, or cycloalkyl, cycloalkenyl, aryl, saturated carbon ring-condensed aryl, saturated heterocyclic ring-condensed aryl, heteroaryl or 5- to 8-membered monocyclic saturated heterocyclic ring, which may be substituted with 1 to 4 substituents selected from the group D1, and Rd and Re may be the same or different from each other and each represents -H, -lower alkyl, -halogen, -OH or -O-lower alkyl.)

[0029] Among compounds (I) of the invention, preferred compounds are shown below.

1. A compound in which R^1 and R^2 may be the same or different from each other and each represents -H, -lower alkyl, -lower alkenyl, -lower alkynyl, -NRaRb, -NRc-NRaRb, -(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -NRc-C(=NH)-NRaRb, -NRaCORb, -MRaCO-ORb, -NRaCO-NRbRc, -NRa-CO-lower alkylene-NRbRc or -NRaCO-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl),
A is aryl which may have 1 to 5 substituents selected from the group D, heteroaryl which may have 1 to 5 substituents selected from the group D, saturated carbon ring-condensed aryl which may have 1 to 5 substituents selected from the group D or saturated heterocyclic ring-condensed aryl which may have 1 to 5 substituents selected from the group D, and R^3 is cycloalkyl which may have 1 to 5 substituents selected from the group D, cycloalkenyl which may have 1 to 5 substituents selected from the group D, aryl which may have 1 to 5 substituents selected from the group D, saturated carbon ring-condensed aryl which may have 1 to 5 substituents selected from the group D, saturated heterocyclic ring-condensed aryl which may have 1 to 5 substituents selected from the group D, heteroaryl which may have 1 to 5 substituents selected from the group D or 5- to 8-membered monocyclic saturated heterocyclic ring which may have 1 to 5 substituents selected from the group D.

2. A compound in which A is an aryl selected from phenyl and naphthyl; a heteroaryl selected from benzofuranyl, benzothienyl, benzothiadiazolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzoimidazolyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, benzodioxolyl, imidazopyridyl and indolidinyl groups; a saturated carbon ring-condensed aryl selected from 4-indanyl, 5-indanyl, 5,6,7,8-tetrahydronaphthalen-1-yl and 5,6,7,8-tetrahydronaphthalen-2-yl; or a saturated heterocyclic ring-condensed aryl selected from 3,4-dihydro-2H-1,4-benzoxadinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxynyl, chromanyl, isochromanyl, 3,4-dihydro-2H-1-benzothiopyranyl, 3,4-dihydro-1H-2-benzothiopyranyl, indolinyl, isoindolinyl, 1,2,3,4-tetrahydroquinolyl and 1,2,3,4-tetrahydroisoquinolyl groups, wherein the aforementioned aryl, heteroaryl, saturated carbon ring-condensed aryl or saturated heterocyclic ring-condensed aryl may have 1 to 4 substituents respectively selected from the group D1, and
R^3 is cycloalkyl which may have 1 to 4 substituents selected from the group D1, cycloalkenyl which may have 1 to 4 substituents selected from the group D1, aryl which may have 1 to 4 substituents selected from the group D1, saturated carbon ring-condensed aryl which may have 1 to 4 substituents selected from the group D1, saturated heterocyclic ring-condensed aryl which may have 1 to 4 substituents selected from the group D1, heteroaryl which may have 1 to 4 substituents selected from the group D1 or 5- to 8-membered monocyclic saturated heterocyclic ring which may have 1 to 4 substituents selected from the group D1.

3. A compound in which A is aryl which may have 1 to 4 substituents selected from the group D1, heteroaryl which may have 1 to 4 substituents selected from the group D1 or saturated heterocyclic ring-condensed phenyl which may have 1 to 4 substituents selected from the group D1, and
R^3 is cycloalkyl which may have 1 to 4 substituents selected from the group D1, cycloalkenyl which may have 1 to 4 substituents selected from the group D1, aryl which may have 1 to 4 substituents selected from the group D1, saturated heterocyclic ring-condensed phenyl which may have 1 to 4 substituents selected from the group D1 or

5- to 7-membered monocyclic saturated heterocyclic ring which may have 1 to 4 substituents selected from the group D1.

4. A compound in which X is CO.

5. A compound in which R^1 is $-NH_2$ and R^2 is -H.

6. A compound in which A is a group selected from phenyl, benzothienyl, benzothiadiazolyl, benzothiazolyl, indolyl, quinolyl and 5-indanyl, which may have 1 or 2 substituents selected from the group consisting of -lower alkyl, $-CF_3$, -halogen, -OH, -SH, -S-lower alkyl and -O-lower alkyl; or a group selected from 3,4-dihydro-2H-1,4-benzoxadinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxynyl and indolyl groups, which may be substituted with 1 or 2 =O(oxo), and

R^3 is a group selected from cyclohexyl, cyclohexenyl, phenyl, pyridyl, pyrimidinyl, quinolyl and tetrahydro-2H-pyranyl, which may be substituted with 1 or 2 halogen atoms; or a group selected from tetrahydro-2H-thiopyranyl and 3,4-dihydro-2H-1-benzothiopyranyl, which may be substituted with 1 or 2 oxo groups.

7. Compounds listed below or salts thereof.

N-({[4-(2-Aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(2,3-dihydro-1H-indol-6-yl)benzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(1,2,3,4-tetradihydroquinolin-6-yl)benzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-fluorobenzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(1,3-benzodioxol-5-yl)-4-fluorobenzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-benzothiazol-5-yl-4-fluorobenzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-benzothiazol-6-yl-4-fluorobenzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-indan-5-ylbenzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N- (3-hydroxyindan-5-yl) benzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(1H-indol-5-yl)benzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl)benzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(3-oxo-3,4-dihydro-2H-1,4-benzooxazin-6-yl)benzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(1,2,3-benzothiadiazol-5-yl)-4-fluorobenzamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl)tetrahydro-2H-thiopyran-4-carboxamide 1,1-dioxide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-benzothiazol-5-yl-4-fluorocyclohex-3-enecarboxamide,
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-benzothiazol-5-yl-4,4-difluorocyclohexanecarboxamide, and
N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-indan-5-yltetrahydro-2H-thiopyran-4-carboxamide 1,1-dioxide.

[0030] Salts of the compound (I) of the invention are pharmaceutically acceptable salts. Illustrative examples of its acid addition salt include acid addition salts with hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like inorganic acids, and with formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, aspartic acid, glutamic acid and the like organic acids. In addition, there is a case of forming salts with bases depending on the kinds of substituents, and their examples include salts with inorganic bases containing sodium, potassium, magnesium, calcium, aluminum and the like metals, salts with methylamine, ethylamine, ethanolamine, lysine, ornithine and the like organic bases, ammonium salts and the like.

[0031] Depending on the kinds of substituents, there is a case in which the compound (I) of the invention exists, e. g., in cis-trans and the like geometrical isomers or keto-enol and the like tautomers, and separated or mixed substances of these isomers are included in the invention. Also, since the compound of the invention contains asymmetric carbon atom in some cases, isomers based on the asymmetric carbon atom can exist. The invention also includes mixtures and isolated forms of these optical isomers. Also, depending on the kinds of substituents, there is a case in which the compound of the invention forms N-oxide, and these N-oxide compounds are also included in the invention. In addition, the invention also includes various hydrates, solvates and polymorphic substances of the compound (I) of the invention. In this connection, all of the compounds which are metabolized in the living body and converted into compounds having the aforementioned general formula (I) or salts thereof, so-called prodrugs, are included in the compound of the invention. As groups which form the prodrugs of the invention, those groups described in *Prog. Med.*, 5: 2157-2161 (1985) and those described in "Iyakuhin-no Kaihatsu (Development of Drugs)", Vol. 7, Bunshi Sekkei (Molecular De-

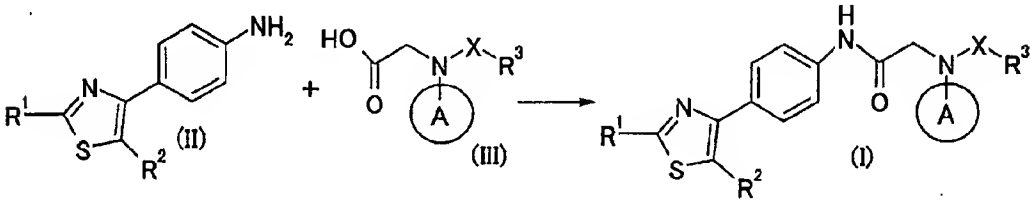
signing), 163 - 198, published in 1990 by Hirokawa Shoten can be exemplified.

(Production Methods)

[0032] Typical production methods of the compound (I) of the invention are described in the following.

[0033] In this connection, depending on the kinds of functional group in the following production methods, there is a case in which substitution of said functional group by an appropriate protecting group, namely a group which can be easily converted into said functional group, at the stage of the material or its intermediate is effective in view of the production techniques. Thereafter, a compound of interest can be obtained by removing the protecting group as occasion demands. Amino group, hydroxyl group, carboxyl group and the like can be exemplified as such functional groups, and as their protecting groups, the protecting groups described in Protective Groups in Organic Synthesis, 3rd Edition (edited by T.W. Green and P.G.M. Wuts, published by JOHN WILLY & SONS, INC.) can for example be cited, which may be optionally used depending on the reaction conditions. The methods described in said textbook can be optionally applied to the introduction of protecting groups and deprotection.

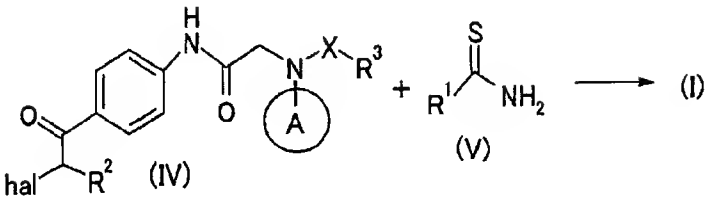
Production method 1



[0034] The compound (I) of the invention can be easily produced by subjecting a carboxylic acid compound (III) and a thiazolylphenyl derivative (II) to amidation reaction.

[0035] The amidation reaction can be carried out by a conventional method, for example, a method described in "Jikken Kagaku Koza (Experimental Chemistry Course)" 4th Edition (Maruzen), vol. 22, pp. 137 - 173, edited by The Chemical Society of Japan, can be employed. Preferably, it can be carried out by converting the carboxylic acid compound (III) into a reactive derivative such as an acid halide (acid chloride or the like) or acid anhydride and then allowing it to react with the thiazolylphenyl derivative (II). When a reactive derivative of the carboxylic acid is used, it is desirable to add a base (sodium hydroxide or the like inorganic base or triethylamine (TEA), diisopropylethylamine, pyridine or the like organic base). In addition, the amidation can also be carried out in the presence of a carboxylic acid activating agent for the carboxylic acid, such as a condensing agent (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC), 1,1'-carbonylbis-1H-imidazole (CDI) or the like). The reaction temperature can be optionally selected depending on the material compounds. Examples of the solvent include reaction-inert solvents such as aromatic hydrocarbon solvents (benzene, toluene and the like), ether solvents (tetrahydrofuran (THF), 1,4-dioxane and the like), halogenated hydrocarbon solvents (dichloromethane, chloroform and the like), amide solvents (N,N-dimethylformamide (DMF), N,N-dimethylacetamide and the like) and basic solvents (pyridine and the like). The solvents are optionally selected based on the kinds of the material compounds and the like, and used alone or as a mixture of two or more.

Production method 2

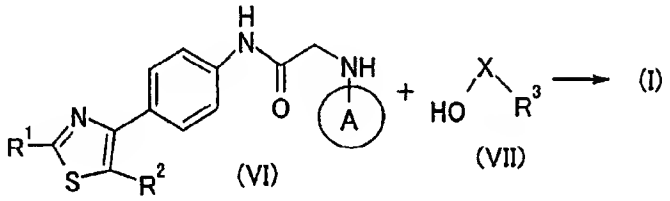


(In the formula, hal represents halogen. The same shall apply hereinafter.)

[0036] This production method is a method in which the compound (I) of the invention is obtained by subjecting an α-ketone halide represented by the general formula (IV) to cyclization reaction with a compound (V). This cyclization reaction can be carried out by a conventional method, and the methods described, e.g., in *Tetrahedron Lett.,* 9, 24, 1959, and The Chemistry of Heterocyclic Compounds "Thiazole and its Derivatives 1 and 2" (edited by J.V. Metzger: John Eiley & Sons) can be employed.

[0037] Preferably, it can be carried out by allowing the material compound α-ketone halide (IV) to react with the compound (V) under cooling to under heating in a solvent or without using solvent. As the solvent, alcohol solvents (methanol, ethanol, isopropanol and the like), carbonyl solvents (acetone, methyl ethyl ketone and the like) and the aforementioned ether solvents, halogenated hydrocarbon solvents and amide solvents and the like can be used preferably. These solvents may be used alone or as a mixture of two or more. The solvent should be optionally selected depending on the kinds of the material compound and the like. When a base (potassium carbonate, sodium carbonate, TEA or the like) is added in carrying out the reaction, the reaction may progress smoothly in some cases.

Production method 3



[0038] This production method is a method in which the compound (I) of the invention is obtained by subjecting an amine compound represented by the general formula (VI) and a carboxylic acid or sulfonic acid compound (VII) to amidation or sulfonamidation reaction.

[0039] The amidation reaction can be carried out in the same manner as in the production method 1.

[0040] The sulfonamidation reaction can be carried out in the usual way by allowing a sulfonic acid reactive derivative of the compound (VII) to react with the amine compound (VI). As the reactive derivative of sulfonic acid, an acid halide (acid chloride, acid bromide or the like), an acid anhydride (sulfonic anhydride prepared from two molecules of sulfonic acid), an acid azide and the like can be exemplified. These reactive derivatives of sulfonic acid can be obtained easily from corresponding sulfonic acids in accordance with a usually used general method. When an acid halide is used as the reactive derivative, it is desirable to carry out the reaction in the presence of a base (sodium hydroxide, sodium hydride or the like inorganic base or pyridine, TEA, diisopropylethylamine or the like organic base). When reacted with an acid anhydride, acid azide or the like reactive derivative, the reaction can be carried out in the absence of a base. In some cases, the reaction may be carried out in the presence of sodium hydride or the like inorganic base or TEA, pyridine, 2,6-lutidine or the like organic base. The reaction temperature is optionally selected depending on the kinds of the sulfonic acid reactive derivative and the like. As the solvent, a reaction inert solvent such as the solvent exem-

plified for the amidation of the aforementioned production method 1 can be used.

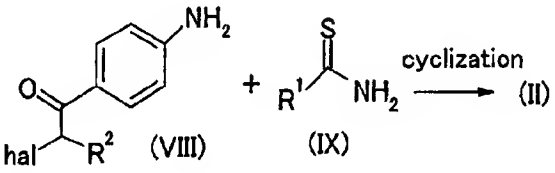
[0041] In addition, depending on the kinds of substituents, a desired compound of the invention can be produced by further subjecting to a substituent group modification reaction well known to those skilled in the art. For example, known reactions such as the aforementioned amidation and sulfonamidation and the N-alkylation described in "Jikken Kagaku Koza (Maruzen), published by The Chemical Society of Japan, can be optionally employed. Also, the reaction sequence may be optionally changed depending on the compound of the interest and kinds of reaction to be employed.

Production Methods of Material Compounds

[0042] Each of the aforementioned material compounds can be easily produced by using known reactions, e.g., the reactions described in "Jikken Kagaku Koza (Maruzen), published by The Chemical Society of Japan. Their typical production methods are shown below.

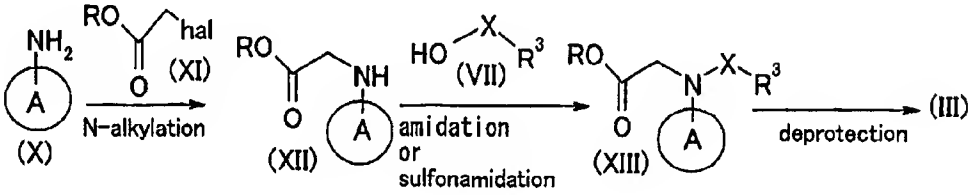
Production Method of Compound (II)

[0043]



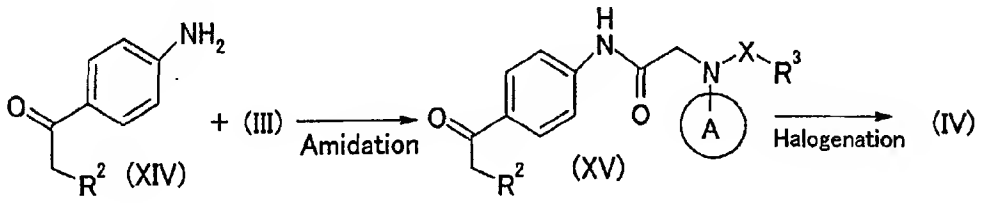
Production Method of Compound (III)

[0044]



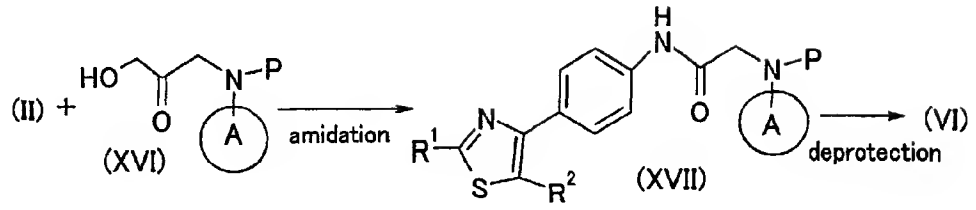
Production Method of Compound (IV)

[0045]



Production Method of Compound (VI)

[0046]



(In the formulae, R means a group which can form an ester residue such as a lower alkyl, aralkyl or the like, and P means an amino group-protecting group such as fluorenylmethoxycarbonyl (Fmoc) or the like.)

[0047] In the above reaction schemes, the amidation can be carried out in the same manner as the method described in the aforementioned production method 1, and the cyclization in the same manner as the method described in the production method 2, and the sulfonamidation in the same manner as the method described in the production method 3.

[0048] The N-alkylation of compound (X) can be carried out using an alkyl halide compound (XI) by a conventional method such as the method described in the aforementioned "Jikken Kagaku Koza, 4th edition (Maruzen), vol. 20, pp. 279 - 318. The reaction can be carried out at a reaction temperature of from cooling to heating, and examples of the solvent include reaction-inert solvents such as the solvents exemplified for the amidation in the aforementioned production method 1. It is desirable to carry out the reaction in the presence of potassium carbonate, sodium hydroxide, sodium hydride or the like base.

[0049] The deprotection for obtaining the carboxylic acid compound (III) can be carried out by optionally employing a conventional method depending on the kinds of ester. Preferably, it can be carried out by treating with a base such as sodium hydroxide aqueous solution in the case of ethyl ester or the like alkyl ester, or by reducing with palladium-carbon (Pd-C) in an atmosphere of hydrogen in the case of benzyl ester or the like aralkyl ester. The reaction can be carried out in accordance with the aforementioned method described in Protective Groups in Organic Synthesis, 3rd Edition.

[0050] The α-ketone halide compound (IV) can be synthesized by the halogenation of an acyl compound (XV) in the usual way. Examples of the halogenation reagent include chlorine, bromine, iodine, copper(II) bromide, potassium iodate, benzyltrimethylammonum tribromide, phenyltrimethylammonium tribromide, tetrabutylammonium tribromide, sulfuryl chloride, trimethylsilyl chloride, trimethylsilyl bromide, 5,5-dibromobarbituric acid and the like, and examples of the solvent include reaction-inert solvents such as acetic acid, hydrobromic acid/acetic acid and the like acidic solvents and the aforementioned alcohol solvents and ether solvents. The reaction can be carried out at a reaction temperature of from cooling to heating.

[0051] The deprotection for obtaining the amine compound (VI) can be carried out by optionally employing a conventional method depending on the kinds of protecting groups. For example, the method described in the aforementioned Protective Groups in Organic Synthesis, 3rd Edition, 503 - 572, can be employed.

[0052] In addition, depending on the kinds of substituents, a desired material compound can be produced by further subjecting to a substituent group modification reaction well known to those skilled in the art.

[0053] The compound of the invention obtained in this manner is isolated and purified directly as its free form or as a salt thereof after carrying out a salt formation treatment by a conventional method. The isolation and purification are carried out by employing extraction, evaporation, crystallization, filtration, recrystallization, various chromatographic techniques and the like general chemical operations.

[0054] Various isomers can be isolated by conventional methods making use of the difference in physicochemical properties between isomers. For example, a racemic compound can be converted into a three-dimensionally pure isomer by a general optical resolution method [e.g., a method in which it is converted into a diastereomer salt with a general optically active acid (tartaric acid or the like) and then subjected to optical resolution]. Also, a mixture of diastereomers can be separated, for example, by fractional crystallization or a chromatography. In addition, an optically active compound can also be produced by the use of an appropriate optically active material.

Industrial Applicability

[0055] Since the compound (I) of the invention has excellent anti-VZV activity, it is useful as a medicament, particularly as an anti-herpesvirus agent or the like viral agent, for the prevention or treatment of varicella (chickenpox) accompa-

nied by VZV infection and shingles accompanied by the recurrent infection of latent VZV.

[0056] In addition, since the compound of the invention also has the activity to inhibit replication of other herpesviruses (HSV-1, HSV-2 and the like), it can also be applied to the prevention or treatment of various herpesvirus infections such as herpes labialis and herpes encephalitis accompanied by HSV-1 infection and genital herpes accompanied by HSV-2, so that it is useful as an general-purpose anti-herpesvirus agent.

[0057] Pharmacological actions of the compound of the invention were confirmed by the following pharmacological tests.

Test Example 1 Anti-VZV activity assay

[0058] This assay was carried out in accordance with the method described by Shigeta S. (*The Journal of Infectious Diseases,* 147, 3, 576 - 584 (1983). Illustratively, HEF cells were seeded a 96 well microtiter plate at 10,000 cells per well using a propagation medium and cultured at 37°C for 4 days in an atmosphere of 5% CO_2 until monolayers were formed. After washing the cells with a maintaining medium, the cells were inoculated with 100 μl/well of VZV (strain CaQu) which had been diluted to 20 to 30 pfu/100 μl with the maintaining medium. The plate was centrifuged at 2,000 rpm for 20 minutes at room temperature and then incubated at 37°C for 3 hours in an atmosphere of 5% CO_2 to infect with VZV. After washing three times with 100 μl/well of the maintaining medium, 100 μl of each test drug diluted to an appropriate concentration with the maintaining medium was added to each well. After culturing the cells at 37°C for 3 to 4 days in an atmosphere of 5% CO_2, the cells were fixed with 100 μl/well of 10% formalin/PBS for 2 to 3 hours. After discarding the fixing solution and culture supernatant and subsequently washing the plate with water, a staining solution (0.025% Crystal Violet) was added in 50 μl/well to carry out 2 to 3 minutes for staining, and then the plate was washed with water and dried at 37°C. The HEF cells infected with VZV cause cell death, and plaques comprising dead cells are formed in the monolayer HEF cells. The number of plaques was counted under a microscope, and EC_{50} value of the test drug was calculated as a concentration to inhibit 50% of the plaques.

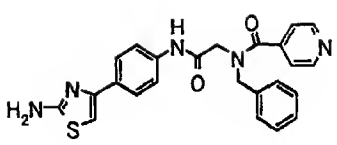
[0059] The EC_{50} values (μM) of the compounds of the invention are shown in the following table. The compounds of the invention were possessed of excellent anti-viral activity against VZV in comparison with acyclovir and known thiazolylphenyl derivatives (Comparative Compounds a and b).

Table 1

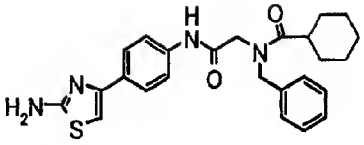
Test compound	EC_{50}	Test compound	EC_{50}	Test compound	EC_{50}
Example 7	0.046	Example 21	0.062	Example 25	0.067
Example 32	0.094	Example 39	0.042	Example 40	0.038
Example 42	0.087	Example 43	0.031	Example 44	0.030
Example 50	0.059	Example 52	0.042	Example 53	0.065
Example 54	0.034	Example 55	0.055	Example 56	0.041
Example 58	0.049	Example 60	0.081	Example 61	0.046
Example 67	0.081	Example 76	0.095	Example 83	0.043
Example 85	0.090	Example 103	0.12	Example 104	0.52
Example 107	0.025	Example 109	0.049	Example 110	0.026
Example 112	0.040	Example 113	0.070	Example 114	0.028
Example 115	0.033	Example 116	0.065	Example 117	0.059
ACV	4.3	Comp. Comp. a	3.0	Comp. Comp. b	1.1

ACV: acyclovir

Comparative Compounds a and b: compounds of entry Nos. 29 and 34 in Table 1 of WO 97/24343



Comparative Compound a



Comparative Compound b

Test Example 2 Cutaneous HSV-1 infection mouse model (in vivo test)

[0060] Using a cutaneous HSV-1 infection mouse model prepared in accordance with the method of H. Machida *et al. (Antiviral Res.*, 1992, 17, 133 - 143), *in vivo* activity of the compounds of the invention was tested. The skin of each HR-1 hairless mouse was scratched lengthwise and breadthwise several times using a needle and a virus suspension (HSV-1 strain WT-51, 1.5 x 10^4 PFU) was droped to the scarified region for infection. A compound of the invention (the compound of Example 49 or the compound of Example 87) was made into a methyl cellulose suspension and orally administered at a dose of 25 mg/kg twice a day for 5 days. Symptoms of the skin lesion caused by the HSV-1 infection were scored into 7 degrees and evaluated for 21 days, and survived days of mice were also examined.

[0061] As a result, in the placebo group, increase in the score was observed on and after 4th day of the infection due to worsening of the symptoms of the skin lesion, the average lesion score exceeded 6 on the 7th day, and the number of survived days was 10 days or less. On the other hand, in the group in which the compound of the invention was administered, development of skin lesion was inhibited almost completely, and the lesion score was 1 or less during the evaluation period. Also, prolongation of survived days was found and mortal case was not found during the evaluation period.

[0062] Thus, it was confirmed that the compound of the invention has also excellent anti-herpesvirus activity *in vivo*.

[0063] The pharmaceutical composition of the invention which contains one or two or more of the compounds represented by the general formula (I) as the active ingredient can be prepared by generally used methods using pharmaceutical carriers, fillers and the like which are generally used in this field. Its administration may be either oral administration by tablets, pills, capsules, granules, powders, solutions and the like, or parenteral administration by intravenous, intramuscular and the like injections, suppositories, eye drops, eye ointments, inhalations and the like.

[0064] As the solid composition for oral administration according to the invention, tablets, powders, granules and the like are used. In such a solid composition, one or more active substances are mixed with at least one inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate or the like. In the usual way, the composition may contain inert additives such as magnesium stearate or the like lubricant, sodium carboxymethylstarch or the like disintegrating agent and solubilization assisting agent. If necessary, tablets or pills may be coated with a sugar or a gastric or enteric coating agent.

[0065] The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contains a generally used inert diluent such as purified water or ethyl alcohol. In addition to the inert diluent, this composition may also contain a solubilizing agent, a moistening agent, a suspending agent and the like auxiliary agents, as well as sweeteners, flavors, aromatics and preservatives.

[0066] The injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Examples of the aqueous solution include distilled water for injection and physiological saline. Examples of the non-aqueous solution include propylene glycol, polyethylene glycol, olive oil or the like plant oil, ethyl alcohol or the like alcohol, polysorbate 80 (trade name) and the like. Such a composition may further contain a tonicity agent, an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizing agent and a solubilization assisting agent. These are sterilized by, e.g., filtration through a bacteria retaining filter, blending of a germicide or irradiation. Alternatively, they may be used by firstly making into sterile solid compositions and dissolving or suspending them in sterile water or a sterile solvent for injection prior to their use.

[0067] In general, daily dose in the case of oral administration is from about 0.001 to 50 mg/kg body weight, preferably from 0.01 to 30 mg/kg, and daily dose in the case of parenteral administration is from about 0.0001 to 10 mg/kg body weight, and the daily dose is divided into 1 to several doses per day. The dosage is optionally decided by taking into consideration symptoms, age, sex and the like in response to each case.

Best Mode for Carrying Out the Invention

[0068] The following describes the invention further in detail based on examples. The invention is not limited to those described in the following examples. In this connection, production examples of material compounds of the compounds of the invention are shown in Reference Examples.

[0069] Reference Example 1: Potassium carbonate and ethyl bromoacetate were added to DMF solution of aniline and stirred under heating. After adding water and ethyl acetate to the reaction mixture, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure to obtain a crude product. This was dissolved in chloroform, mixed with TEA, 4-fluorobenzoyl chloride and dimethylaminopyridine (DMAP) and stirred. After adding 1 M hydrochloric acid to the reaction solution, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by a silica gel column chromatography (to be referred to as SCG hereinafter), ethyl [(4-fluorobenzoyl)phenylamino]acetate (colorless oil) was obtained.

[0070] Reference Example 2: Potassium carbonate and benzyl bromoacetate were added to DMF solution of ethyl (4-aminophenoxy)acetate and stirred under heating. After adding water and ethyl acetate to the reaction mixture, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. Dichloromethane solution of the thus obtained crude product was mixed with TEA, 4-fluorobenzoyl chloride was added dropwise thereto under ice-cooling and then the reaction solution was stirred. After adding 1 M hydrochloric acid to the reaction solution, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, ethyl {4-[benzyloxycarbonylmethyl-(4-fluorobenzoyl)amino]phenoxy}acetate (colorless oil) was obtained.

[0071] Reference Example 3: A mixture of 6-aminoquinoline, di-tert-butyl dicarbonate and DMAP was stirred under heating. 1,4-Dioxane and 1 M sodium hydroxide aqueous solution were added the reaction mixture and stirred. Ethyl acetate was added to the reaction solution, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, 6-(tert-butyloxycarbonyl)aminoquinoline was obtained. This was dissolved in ethanol, mixed with 20% palladium hydroxide-carbon and stirred in an atmosphere of hydrogen. After filtering the reaction solution, the solvent was evaporated under a reduced pressure to obtain a tetrahydroquinoline compound. This was dissolved in 1,4-dioxane, mixed with 9H-fluorenyl-9-ylmethyl chloroformate and 10% sodium bicarbonate aqueous solution and then stirred. By adding ethyl acetate and water to the reaction solution, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. The residue was dissolved in chloroform, mixed with trifluoroacetic acid and stirred. The solvent was evaporated under a reduced pressure, the residue was mixed with ethyl acetate, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, 9*H*-fluorenyl-9-ylmethyl 6-amino-1,2,3,4-tetrahydroquinoline-1-carboxylate was obtained. This was dissolved in acetonitrile, mixed with potassium carbonate and benzoyl bromoacetate and then stirred under heating. The reaction mixture was filtered, and the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG. This was dissolved in pyridine, mixed with dichloromethane and 4-fluorobenzoyl chloride and then stirred. After adding ethyl acetate and water to the reaction mixture, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, ethyl {[1-(9*H*-fluorenyl-9-ylmethyloxycarbonyl)-1,2,3,4-tetrahydroquinolin-6-yl](4-fluorobebzoyl)amino}acetate (pale yellow foam) was obtained.

[0072] Reference Example 4: Potassium carbonate and ethyl bromoacetate were added to DMF solution of 6-amino-1-indanone and stirred under heating. After addition of ethyl acetate to the reaction mixture and subsequent filtration, the organic layer was washed and dried, and then the solvent was evaporated under a reduced pressure to obtain an ester compound. This was dissolved in chloroform, mixed with TEA and 4-fluorobenzoyl chloride and then stirred. Subsequently, the reaction solution was mixed with TEA and 4-fluorobenzoyl chloride and then stirred. After addition of ethyl acetate to the reaction solution and subsequent filtration, the solvent of the mother liquid was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG. This was dissolved in ethanol and stirred by adding sodium borohydride. Subsequently, the reaction solution was mixed with sodium borohydride and methanol and stirred. The reaction solution was mixed with water and chloroform, the organic layer was separated, washed and dried, the solvent was evaporated under a reduced pressure, and then the thus obtained crude product was purified by SCG to obtain ethyl [(4-fluorobenzoyl)(3-hydroxyindan-5-yl)amino]acetate (yellow oil).

[0073] Reference Example 5: A mixture of 2-chloropyridine and ethyl aminoacetate hydrochloride was stirred under heating. After addition of ethyl acetate and saturated sodium bicarbonate aqueous solution to the reaction mixture and subsequent separation, the organic layer was washed and dried, and the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG. This was dissolved in dichloromethane and stirred by adding pyridine, 4-fluorobenzoyl chloride and DMAP. The reaction solution was mixed with ethyl acetate and water, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure.

The thus obtained crude product was purified by SCG to obtain ethyl [(4-fluorobenzoyl)(2-pyridyl)amino]acetate (colorless oil).

[0074] Reference Example 6: A chloroform solution of ethyl [(4-piperidinecarbonyl)(4-methoxyphenyl) amino] acetate was stirred by adding acetic acid, sodium triacetoxyborohydride and 36% formaldehyde aqueous solution. And furthermore, the reaction solution was stirred by adding sodium triacetoxyborohydride and 36% formaldehyde aqueous solution. The reaction solution was neutralized by adding saturated sodium bicarbonate aqueous solution, the organic layer was separated by adding chloroform, washed and dried, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG to obtain ethyl {[(1-methyl-4-piperidine)carbonyl] (4-methoxyphenyl)amino)acetate (colorless oil).

[0075] Reference Example 7: Thionyl chloride was added to 1,4-dioxane solution of (1-benzyloxycarbonyl-4-piperidine)carboxylic acid and stirred, and the solvent was evaporated under a reduced pressure. The residue was dissolved in chloroform and stirred by adding ethyl [(4-methoxyphenyl)amino]acetate and TEA, and then the solvent was evaporated under a reduced pressure. The residue was diluted with ethyl acetate, washed and dried, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG. This was dissolved in ethanol, mixed with 5% Pd-C and then stirred at room temperature in an atmosphere of hydrogen. After filtration of the reaction solution, the solvent was evaporated under a reduced pressure to obtain ethyl [(4-piperidinecarbonyl) (4-methoxyphenyl)amino]acetate. This was dissolved in THF and stirred by adding di-tert-butyl dicarbonate and TEA. The reaction solution was stirred by adding 1 M sodium hydroxide aqueous solution and then stirred by adding 1 M sodium hydroxide aqueous solution and ethanol. The reaction solution was mixed with 1 M hydrochloric acid and extracted with chloroform-ethanol (10/1), the organic layer was dried and then the solvent was evaporated under a reduced pressure to obtain {[(1-tert-butyloxycarbonyl-4-piperidine)carbonyl](4-methoxyphenyl)amino}acetic acid (colorless amorphous).

[0076] Reference Example 8: A chloroform solution of ethyl [(4-methoxyphenyl)-(tetrahydrothiopyran-4-carbonyl) amino]acetate was stirred by adding 3-chloroperbenzoic acid (>65%; MCPBA). Sodium bicarbonate aqueous solution was added to the reaction mixture, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, ethyl [(4-methoxyphenyl) -(1-oxo-tetrahydrothiopyran-4-carbonyl)amino]acetate (pale brown foam) was obtained.

[0077] Reference Example 9: A DMF solution of ethyl 4-hydroxycyclohexane carboxylate and 4-chlorobenzyl bromide was mixed with NaH and stirred. The reaction solution was mixed with 10% ammonium chloride and ethyl acetate, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, ethyl 4-cis-(4-chlorobenzyloxy)cyclohexanecarboxylate and then ethyl 4-*trans*-(4-chlorobenzyloxy)cyclohexanecarboxylate were obtained. An ethanol solution of the latter was mixed with 1 M sodium hydroxide aqueous solution and stirred. After adjusting the reaction solution was acidified with 1 M hydrochloric acid, the organic layer was separated by adding chloroform, washed and dried, and then the solvent was evaporated under a reduced pressure. By washing the thus obtained crude product with diisopropyl ether, 4-trans-(4-chlorobenzyloxy)cyclohexanecarboxylic acid was obtained. A dichloromethane solution of this was mixed with one drop of DMF and oxalyl chloride and stirred. Saturated sodium bicarbonate aqueous solution and chloroform were added to the reaction solution to separate the organic layer. The thus obtained crude product was purified by SCG. Its ethyl acetate solution was mixed with 5% Pd-C and stirred in an atmosphere of hydrogen. The reaction solution was filtered and then the solvent was evaporated under a reduced pressure to obtain [(4-trans-hydroxycyclohexanecarbonyl)(4-methoxyphenyl)amino]acetic acid (colorless solid).

[0078] Reference Example 10: A chloroform solution of ethyl [(4-methoxyphenyl)-(tetrahydrothiopyran-4-carbonyl) amino]acetate was mixed with MCPBA and stirred. After adding sodium bicarbonate aqueous solution to the reaction mixture, the organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, ethyl [(4-methoxyphenyl)-(1,1-dioxo-tetrahydrothiopyran-4-carbonyl)amino]acetate (white foam) was obtained.

[0079] Reference Example 11: A chloroform solution of tert-butyl [4-(4-{2-[(9H-fluoren-9-ylmethoxycarbonyl)-(4-methoxyphenyl)amino]acetylamino}phenyl)thiazol-2-yl]carbamate was mixed with piperidine and stirred. The thus precipitated precipitate was filtered and then washed to obtain tert-butyl (4-{4-[2-(4-methoxyphenylaminoacetylamino)phenyl] thiazol-2-yl}carbamate (white solid).

[0080] Reference Example 12: An ethanol solution of ethyl [(4-fluorobenzoyl)-(4-fluorophenyl)amino]acetate was mixed with 3 M sodium hydroxide aqueous solution and heated under reflux. The reaction solution was concentrated, the residue was mixed with 1 M hydrochloric acid and chloroform, the organic layer was separated, washed and dried and then the solvent was evaporated under a reduced pressure. A dichloromethane solution of the thus obtained carboxylic acid crude product was mixed with 4-aminoacetophenone and WSC·HCl in that order and then stirred. The reaction solution was mixed with 1 M hydrochloric acid, the organic layer was separated, washed and dried and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, N-[(4-acetyl-phenylcarbamoyl)methyl]-4-fluoro-N-(4-fluorophenyl)benzamide (white foam) was obtained.

[0081] Reference Example 13: An ethanol solution of methyl N-[(4-acetylphenylcarbamoyl)methyl]-N-(4-fluorophenyl)terephthalamate was mixed with 1 M sodium hydroxide aqueous solution and heated under reflux. The reaction solution was concentrated, 1 M hydrochloric acid and chloroform were added to the residue, the organic layer was separated, washed and dried and then the solvent was evaporated under a reduced pressure. A toluene suspension of the thus obtained carboxylic acid crude product was mixed with thionyl chloride and a small amount of DMF and heated under reflux. After evaporating the solvent under a reduced pressure, the residue was dissolved in dichloromethane, and the solution was mixed with 28% aqueous ammonia under ice-cooling and stirred at the same temperature. The organic layer was separated, washed and dried, and then the solvent was evaporated under a reduced pressure. By purifying the thus obtained crude product by SCG, N-[(4-acetylphenylcarbamoyl)methyl]-N-(4-fluorophenyl)terephthalamide (pale yellow solid) was obtained.

[0082] Reference Examples 14 to 99: The compounds of Reference Examples 14 to 38, 40 and 42 to 97 shown in Tables 2 to 6 describing later were obtained in the same manner as in Reference Example 1, the compounds of Reference Examples 39 and 41 shown in Table 2 describing later were obtained in the same manner as in Reference Example 2, the compound of Reference Example 98 shown in Table 6 describing later were obtained in the same manner as in Reference Example 4, and the compounds of Reference Examples 99 and 100 shown in Table 7 describing later were obtained in the same manner as in Reference Example 12.

[0083] Example 1: Ethanol (10 ml) solution of ethyl [(4-fluorobenzoyl)phenylamino]acetate (599 mg) was mixed with 1 M sodium hydroxide aqueous solution (2.3 ml) and then stirred at room temperature for 5 hours. After changing liquid property of the reaction solution to acidic by adding 1 M hydrochloric acid, water and chloroform were added thereto and the organic layer was separated. Subsequently, the organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. After dissolving the thus obtained crude carboxylic acid in DMF (15 ml), 4-(4-aminophenyl)thiazol-2-ylamine dihydroiodide (831 mg), pyridine (0.23 ml), HOBt (0.3 g) and WSC·HCl (0.42 g) were added thereto in that order and stirred at room temperature for 22 hours. After adding 1 M sodium hydroxide aqueous solution and ethyl acetate to the reaction solution, the organic layer was separated. Subsequently, the organic layer was washed with saturated brine, dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 97/3) to obtain 451 mg of yellow foam. This was dissolved in chloroform-methanol (4 ml-1 ml) and mixed with 4 M hydrogen chloride in ethyl acetate (0.38 ml), and then the solvent was evaporated under a reduced pressure. By recrystallizing the thus obtained crude crystals from ethanol, 270 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-phenylbenzamide monohydrochloride (pale yellow crystals) was obtained.

[0084] Example 2: Ethanol-chloroform (20 ml-10 ml) solution of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(4-methanesulfanylphenyl)benzamide (445 mg) was mixed with MCPBA (0.35 g) and then stirred at room temperature for 1 hour. The reaction solution was mixed with saturated sodium bicarbonate aqueous solution (40 ml) and chloroform (10 ml) and then stirred at room temperature for 5 hours. After adding chloroform to the reaction solution, the organic layer was separated, dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 95/5) to obtain 217 mg of a yellow oily substance. This was dissolved in chloroform-methanol (3 ml-3 ml) and mixed with 4 M hydrogen chloride in ethyl acetate (0.35 ml), and then the solvent was evaporated under a reduced pressure. By washing the thus obtained crude product with ethyl acetate, 80 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(4-methanesulfinylphenyl)benzamide monohydrochloride (pale yellow foam) was obtained.

[0085] Example 3: Ethyl ether (50 ml) solution of ethyl 4-[ethoxycarbonylmethyl(4-fluorobenzoyl)amino]benzoate (700 mg) was mixed with potassium trimethylsilanolate (0.29 g, 90%) and then stirred at room temperature for 24 hours. After collecting the precipitate by filtration and dissolving in water, liquid property of the solution was changed to acidic by adding 1 M hydrochloric acid, and the organic layer was separated by adding chloroform. Subsequently, the organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. After dissolving the thus obtained crude carboxylic acid in DMF (10 ml), 4-(4-aminophenyl)thiazol-2-ylamine dihydroiodide (358 mg), pyridine (0.09 ml), HOBt (0.16 g) and WSC·HCl (0.23 g) were added thereto in that order and stirred at room temperature for 3 days. After adding saturated sodium bicarbonate aqueous solution and ethyl acetate to the reaction solution, the organic layer was separated. Subsequently, the organic layer was washed with saturated brine, dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 98/2) to obtain 130 mg of a colorless foam. A chloroform-ethanol (2 ml-2 ml) solution of this compound (62 mg) was mixed with 4 M hydrogen chloride in ethyl acetate (0.1 ml), and then the solvent was evaporated under a reduced pressure. By washing the thus obtained crude product with ethyl acetate, 42 mg of N-[({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-(4-fluorobenzoyl)amino]benzoate monohydrochloride (amorphous solid) was obtained.

[0086] Example 4: Ethanol (100 ml) solution of ethyl {4-[benzyloxycarbonylmethyl-(4-fluorobenzoyl)amino]phenoxy}acetate (6.4 g) was mixed with 10% Pd-C (500 mg) and then stirred at room temperature overnight in an atmosphere of hydrogen. After removing PD-C by celite, the filtrate was concentrated. After dissolving the thus obtained crude

carboxylic acid in DMF (80 ml), 4-(4-aminophenyl)thiazol-2-ylamine dihydroiodide (5.5 g), pyridine (1.8 ml), HOBt (2.6 g) and WSC·HCl (3.7 g) were added thereto in that order and stirred at room temperature for 3 hours. After adding 10% potassium carbonate aqueous solution and ethyl acetate to the reaction solution, the organic layer was separated. Subsequently, the organic layer was washed twice with 5% brine, washed with saturated brine, dried with anhydrous magnesium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 97/3 → 95/5) to obtain 2.0 g of yellow foam. A chloroform-ethanol (20 ml-5 ml) solution of this compound (900 mg) was mixed with 4 M hydrogen chloride in ethyl acetate (0.6 ml), and then the solvent was evaporated under a reduced pressure. By recrystallizing the thus obtained crude crystals from ethanol, 540 mg of ethyl {4-N-({[4-(2-aminothiazol-4-yl)phenyl] carbamoyl}methyl)-N- (4-fluorobenzoyl)amino} phenoxy}acetate monohydrochloride (white crystals) was obtained.

[0087] Example 5: Ethanol-THF (50 ml-10 ml) solution of ethyl {[4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl] -(4-fluorobenzoyl)amino}acetate (2.4 g) was mixed with 1 M sodium hydroxide aqueous solution (9.9 ml) and then stirred under heating at 60°C for 1 hour. After concentration of the reaction solution, the residue was mixed with 1 M hydrochloric acid and chloroform to separate the organic layer. The organic layer was washed with saturated brine, dried with anhydrous magnesium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. After dissolving the thus obtained crude carboxylic acid in DMF (50 ml), 4-(4-aminophenyl)thiazol-2-ylamine dihydroiodide (1.5), pyridine (0.4 ml), HOBt (580 mg) and WSC·HCl (820 mg) were added thereto in that order and stirred at room temperature for 3 hours. After adding 10% potassium carbonate aqueous solution and ethyl acetate to the reaction solution, the organic layer was separated. Subsequently, the organic layer was washed twice with 5% brine, washed with saturated brine, dried with anhydrous magnesium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was dissolved in chloroform (30 ml), mixed with trifluoroacetic acid (15 ml) and then stirred at room temperature for 3 hours. After concentration of the reaction solution, 10% potassium carbonate aqueous solution and chloroform were added to the resulting residue, and the organic layer was separated. The organic layer was washed saturated brine, dried with anhydrous magnesium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol/28% aqueous ammonia = 96/4/0.4 → 92/8/0.8) to obtain 210 mg of yellow foam. This was dissolved in chloroform-ethanol (20 ml-5 ml) and mixed with 4 M hydrogen chloride in ethyl acetate (0.4 ml), and then the solvent was evaporated under a reduced pressure. By recrystallizing the thus obtained crude crystals from ethanol, 170 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(4-piperazin-1-ylphenyl)benzamide trihydrochloride (white crystals) was obtained.

[0088] Example 6: Ethanol (30 ml) solution of ethyl {4-[N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl) -N-(4-fluorobenzoyl)amino]phenoxy}acetate (1.3 g) was mixed with 1 M sodium hydroxide aqueous solution (2.4 ml) and then stirred at room temperature overnight. After concentration of the reaction solution, the thus obtained crude product was recrystallized from ethanol to obtain 680 mg of sodium {4-[N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl} methyl)-N-(4-fluorobenzoyl)amino]phenoxy}acetate (white crystals).

[0089] Example 7: Ethanol (50 ml) solution of ethyl {[1-(tert-butyloxycarbonyl)-2,3-dihydro-lH-indol-6-yl](4-fluorobenzoyl)amino}acetate (2.57 g) was mixed with 1 M sodium hydroxide aqueous solution (12 ml) and then stirred at room temperature for 5 hours. The reaction solution was mixed with 1 M hydrochloric acid (12 ml) and extracted with chloroform. The organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. After dissolving the thus obtained carboxylic acid derivative in DMF (100 ml), 4-(4-aminophenyl)thiazol-2-ylamine dihydroiodide (2.24 g), pyridine (0.47 ml), HOBt (0.78 g) and WSC·HCl (1.1 g) were added thereto in that order and stirred at room temperature for 18 hours. After adding 1 M sodium hydroxide aqueous solution and ethyl acetate to the reaction solution, the organic layer was separated. Subsequently, the organic layer was washed with saturated brine, dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 98/2) to obtain N-({ [4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-[1-(tert-butyloxycarbonyl) -2,3-dihydro-1H-indol-6-yl] benzamide. This was dissolved in chloroform (20 ml), mixed with trifluoroacetic acid and stirred at room temperature for 20 minutes. The residue was diluted with ethyl acetate and washed with 1 M sodium hydroxide aqueous solution, the organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was washed with ethyl acetate/hexane/ethanol (12/4/1) to obtain 966 mg of a pale brown solid. Chloroform-ethanol (1/1) solution of this solid matter (398 mg) was mixed with 4 M hydrogen chloride in ethyl acetate (1 ml) and then the solvent was evaporated under a reduced pressure. By washing the thus obtained residue with isopropyl alcohol, 283 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(2,3-dihydro-1H-indol-6-yl)benzamide dihydrochloride (pale brown amorphous solid) was obtained.

[0090] Example 8: Ethyl acetate (70 ml) solution of ethyl {[1-(9*H*-fluorenyl-9-ylmethyloxycarbonyl)-1,2,3,4-tetrahydroquinolin-6-yl](4-fluorobenzoyl)amino}acetate (2.21 g) was mixed with 5% Pd-C (0.22 g) and then stirred at room temperature for 3 hours in an atmosphere of hydrogen. The reaction solution was filtered through celite and then the solvent was evaporated under a reduced pressure. The thus obtained carboxylic acid derivative was dissolved in DMF

(50 ml), and 4-(4-aminophenyl)thiazol-2-ylamine dihydroiodide (1.34 g), pyridine (0.27 ml), HOBt (0.47 g) and WSC·HCl (0.67 g) were added thereto in that order and stirred at room temperature for 5 hours. After adding saturated sodium bicarbonate aqueous solution and ethyl acetate to the reaction solution, the organic layer was separated. The organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 98.5/1.5) to obtain N- ({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-[1-(9*H*-fluorenyl-9-ylmethyloxycarbonyl)-1,2,3,4-tetrahydroquinolin-6-yl]benzamide. This was dissolved in pyrrolidine (12 ml) and stirred at room temperature 2.5 hours. The solvent of the reaction solution was evaporated under a reduced pressure, and the residue was purified by SCG (chloroform/methanol = 98/2) and washed with chloroform-ethyl acetate-hexane-ethanol (24/12/12/1) to obtain a colorless solid. Chloroform-ethanol (4 ml-4 ml) solution of this solid matter (277 mg) was mixed with 4 M hydrogen chloride in ethyl acetate (0.5 ml) and then the solvent was evaporated under a reduced pressure. By recrystallizing the thus obtained crude crystals from isopropyl alcohol, 229 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(1,2,3,4-tetrahydroquinolin-6-yl)benzamide dihydrochloride (pale yellow crystals) was obtained.

[0091] Example 9: A DMF (30 ml) solution of isonicotinic acid (0.12 g) was mixed with CDI (0.16 g) and stirred at room temperature for 10 minutes. A DMF (50 ml) solution of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl)methyl)-4-fluoro-N-(1,2,3,4-tetrahydroquinolin-7-yl)benzamide dihydrochloride (390 mg) was added to the reaction solution at 0°C, and the mixture was gradually warmed to room temperature spending 1 hour while stirring and then stirred at room temperature for 1.5 hours. The reaction solution was mixed with ethyl acetate and washed with a saturated sodium bicarbonate aqueous solution (50 ml)-0.16 M sodium hydroxide aqueous solution (50 ml) mixed solution and then with saturated brine. The organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 95/5) to obtain 293 mg of colorless foam. This was dissolved in chloroform-methanol (10 ml-10 ml), mixed with 4 M hydrogen chloride in ethyl acetate (1 ml) and then the solvent was evaporated under a reduced pressure. By recrystallizing the thus obtained crude crystals from isopropyl alcohol, 253 mg of N-({[4-(2-aminothiazol-4-yl)phenyl] carbamoyl}methyl) -4-fluoro-N- [2- (pyridine-4-carbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]benzamide dihydrochloride (pale yellow crystals) was obtained.

[0092] Example 10: THF (40 ml) solution of N-[(4-acetylphenylcarbamoyl) methyl]-N- (4-fluorobenzoyl)terephtalamide (1.1 g) was mixed with phenyltrimethylammonium tribromide (1.1 g) and then stirred at room temperature for 2 hours. The thus formed precipitate was filtered, and the residue obtained by concentrating the resulting filtrate was dissolved in ethanol-THF (20 ml-10 ml), mixed with thiourea (200 mg) and heated under reflux for 3 hours. After concentration of the reaction solution, 5% potassium carbonate aqueous solution and chloroform were added to the resulting residue to separate the organic layer. The organic layer was washed with saturated brine, dried with anhydrous magnesium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methano128% aqueous ammonia = 90/10/1 → 85/15/1.5) to obtain 380 mg of a pale yellow amorphous solid. By subjecting this to a salt forming reaction using 4 M hydrogen chloride in ethyl acetate, 220 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl)terephthalamide monohydrochloride (pale yellow amorphous solid) was obtained.

[0093] Example 11: Methanol (20 ml) solution of methyl N-({[4-(2-aminothiazol-4-yl)phenyl] carbamoyl}methyl) -N-(4-methoxyphenyl)terephthalamate monohydrochloride (800 mg) was mixed with 1 M sodium hydroxide aqueous solution (1.5 ml) and then heated under reflux for 4 hours. The reaction solution was concentrated, and ethanol (20 ml) and diisopropyl ether (10 ml) were added to the thus obtained residue to effect precipitation of crystals. After filtration, the crystals were washed with diisopropyl ether to obtain 530 mg of sodium N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl)terephthalamate (white crystals).

[0094] Example 12: DMF (20 ml) solution of N-(([4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-methoxymethoxy-N-(4-methoxyphenyl)benzamide (1.1 g) was mixed with 6 M hydrochloric acid (2 ml) and then stirred at room temperature for 3 hours. After adding 10% potassium carbonate aqueous solution and ethyl acetate to the reaction solution, the organic layer was separated. Subsequently, the organic layer was washed twice with 5% brine and then with saturated brine, dried with anhydrous magnesium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 97/3 → 95/5) to obtain 630 mg of white crystals. A chloroform-ethanol (20 ml-5 ml) solution of the crystals was mixed with 4 M hydrogen chloride in ethyl acetate (0.5 ml), and then the solvent was evaporated under a reduced pressure. By recrystallizing the thus obtained crude crystals from ethanol, 470 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-hydroxy-N-(4-methoxyphenyl)benzamide monohydrochloride (white crystals) was obtained.

[0095] Example 13: DMF (50 ml) solution of {[(1-tert-butyloxycarbonyl-4-piperidine)carbonyl](4-methoxyphenyl)amino}acetic acid (1.20 g) was mixed with 4-(4-aminophenyl)thiazol-2-ylamine dihydroiodide (1.03 g), pyridine (0.20 ml), HOBt (0.39 g) and WSC·HCl (0.58 g) in that order and stirred at room temperature for 3 days. After adding ethyl acetate and 1 M sodium hydroxide aqueous solution to the reaction solution, the organic layer was separated. The organic layer was washed with saturated brine, dried with anhydrous sodium sulfate and filtered, and then the solvent was

evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 98.5/1.5). A chloroform (20 ml) solution of the thus obtained amide derivative was mixed with trifluoroacetic acid (20 ml) and stirred at room temperature for 10 minutes, and then the solvent was evaporated under a reduced pressure. The residue was dissolved in ethyl acetate and washed with 1 M sodium hydroxide aqueous solution. The precipitate formed during the washing was dissolved in chloroform-methanol (9/1) and then washed with water. The organic layers were combined, dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was recrystallized from ethanol-ethyl acetate to obtain 160 mg of colorless crystals. The crystals were dissolved in chloroform-ethanol (20 ml-20 ml) and mixed with 4 M-hydrogen chloride in ethyl acetate (0.3 ml), and then the solvent was evaporated under a reduced pressure. The thus obtained foamy matter was redissolved in ethanol and then concentrated, thereby obtaining 150 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl)-4-piperidinecarboxamide dihydrochloride (pale yellow foam).

[0096] Example 14: THF (40 ml) solution of N-[(4-acetylphenylcarbamoyl)methyl]-4-fluoro-N-(4-fluorophenyl)benzamide (2.0 g) was mixed with phenyltrimethylammonium tribromide (2.4 g) and then stirred at room temperature for 2 hours. The thus formed precipitate was filtered, and the residue obtained by concentrating the filtrate was dissolved in ethanol (40 ml), mixed with thioacetamide (480 mg) and then heated under reflux for 1 hour. After concentration of the reaction solution, 1 M sodium hydroxide aqueous solution and chloroform were added to the residue, and the organic layer was separated. The organic layer was washed with saturated brine, dried with anhydrous magnesium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (hexane/ethyl acetate = 2/3) to obtain 1.1 g of 4-fluoro-N-(4-fluorophenyl)-N-({[4-(2-methylthiazol-4-yl)phenyl]carbamoyl}methyl)benzamide (white crystals).

[0097] Example 15: Chloroform (20 ml) solution of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(1,3-benzodioxazol-5-yl)-4-fluorobenzamide (480 mg) was mixed with pyridine (0.32 ml) and acetic anhydride (0.28 ml) and then stirred at room temperature for 14 hours. The reaction solution was further mixed with pyridine (0.32 ml), acetic anhydride (0.28 ml) and DMAP (5 mg) and then stirred at room temperature for 2 hours. After evaporation of the solvent of the reaction solution under a reduced pressure, the residue was dissolved in ethyl acetate and washed with 1 M hydrochloric acid, water, 1 M sodium hydroxide aqueous solution, water, saturated sodium bicarbonate aqueous solution and saturated brine in that order. The organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. By washing the thus obtained crude product with chloroform-methanol (1/1) and then with ethanol, 190 mg of N-({[4-(2-acetylaminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(1,3-benzodioxol-5-yl)-4-fluorobenzamide (colorless solid) was obtained. Example 16: A DMF (10 ml) solution of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(1,3-benzodioxazol-5-yl)-4-fluorobenzamide (750 mg) and N-(tert-butoxycarbonyl)glycine (0.35 g) was mixed with HOBt (0.27 g) and WSC·HCl (0.38 g) in that order and stirred at room temperature for 55 hours. After adding ethyl acetate and water to the reaction solution, the organic layer was separated. Subsequently, the organic layer was washed with saturated brine, dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (hexane/ethyl acetate = 60/40 → 40/60) to obtain 670 mg of tert-butyl (([4-(4-{2-[(1,3-benzodioxazol-5-yl)-(4-fluorobenzoyl)amino]acetylamino}phenyl)thiazol-2-yl]carbamoyl}methyl)carbamate (yellow foam). This compound (640 mg) was dissolved in trifluoroacetic acid-chloroform (8 ml-8 ml) and stirred at room temperature for 10 minutes. After evaporating solvent of the reaction solution under a reduced pressure, the residue was dissolved in chloroform-methanol (10/1) and washed with 0.1 M sodium hydroxide aqueous solution and water in that order. Subsequently, the organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol = 98/2) to obtain 330 mg of pale yellow foam. This was dissolved in chloroform-methanol (8 ml-8 ml) and mixed with 4 M hydrogen chloride in ethyl acetate (0.45 ml), and then the solvent was evaporated under a reduced pressure. By recrystallizing the thus obtained crude crystals from methanol, 196 mg of N-[({4-[2-(2-aminoacetylamino)thiazol-4-yl]phenyl}carbamoyl)methyl]-M-(1,3-benzodioxol-5-yl)-4-fluorobenzamide monohydrochloride (colorless crystals) was obtained.

[0098] Example 17: N-([4-(2-aminothiazol-4-yl)phenylcarbamoyl]methyl}-4-fluoro-N-(4-fluorophenyl)benzamide monohydrochloride (200 mg) was dissolved in a mixed solvent of acetic acid (10 ml) and water (5 ml), mixed with bromine (20 μl) under ice-cooling and then stirred at room temperature for 5 minutes. The reaction solution was concentrated under a reduced pressure, and the residue was dissolved in ethyl acetate (30 ml)-saturated sodium bicarbonate aqueous solution (20 ml). The organic layer was washed with saturated brine, dried with anhydrous sodium sulfate and then concentrated under a reduced pressure. The residue was dissolved in ethyl acetate (5 ml) and mixed with 4 M hydrogen chloride in ethyl acetate solution (0.15 ml), and the thus precipitated solid was collected by filtration, dried and then recrystallized from methanol-ether, thereby obtaining 184 mg of N-{[4-(2-amino-5-bromothiazol-4-yl)phenylcarbamoyl]methyl}-4-fluoro-N-(4-fluorophenyl)benzamide monohydrochloride (colorless powder).

[0099] Example 18: A methanol-chloroform (40 ml-20ml) solution of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-benzothiazol-6-yl-4-oxocyclohexanecarboxyamide (430 mg) was mixed with sodium borohydride (0.19 g) at 0°C and then stirred at room temperature for 1 hour. The reaction solution was mixed with water and extracted with

chloroform, the organic layer was dried with anhydrous sodium sulfate and filtered, and then the solvent was evaporated under a reduced pressure. The thus obtained crude product was purified by SCG (chloroform/methanol/27% aqueous ammonia = 94.8/5/0.2). This was dissolved in chloroform-methanol (10 ml-10 ml) and mixed with 4 M hydrogen chloride in ethyl acetate (1 ml), and then the solvent was evaporated under a reduced pressure. By recrystallizing the thus obtained crude crystals from isopropyl alcohol-ethyl acetate (3/1), 259 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-benzothiazol-6-yl-4-hydroxycyclohexanecarboxyamide monohydrochloride (pale yellow crystals) was obtained.

[0100] Examples 19 to 121: The compounds of Examples 19 to 46, 49 to 62, 64 to 103 and 105 to 121 shown in the following Tables 8 to 18 were obtained in the same manner as in Example 1. Also, the compounds of Examples 47 and 48 were obtained in the same manner as in Example 4, and the compound of Example 63 in the same manner as in Example 7, and the compound of Example 104 in the same manner as in Example 16.

Example 121: <Synthesis by combinatorial chemistry: general synthesis method>

[0101] A pyridine (1.0 ml) solution of tert-butyl (4-{4-[2-(4-methoxyphenylaminoacetylamino)phenyl]thiazol-2-yl}carbamate (13.8 mg, 30 μmol) was mixed with from 40 to 90 μmol of each of various carbonyl chlorides or sulfonyl chlorides and stirred at a temperature of from room temperature to 70°C for a period of from 1 hour to 12 hours. By adding 30 to 50 mg of PS-Tris Amine (a scavenger resin mfd. by Argonote, carrying amount 3.0 to 5.0 mmol/g) and stirring at room temperature for 2 to 5 hours, excess amounts of carbonyl chloride or sulfonyl chloride and chloride ions were captured. The PS-Tris Amine was removed by filtration, and pyridine was evaporated under a reduced pressure from the filtered solution. From 10 to 50 mg of respective N-({[4-(2-tert-butoxycarbonylaminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl)amide or sulfonamide derivatives hardly containing pyridine salt were obtained.

[0102] Each of them was mixed with 0.5 to 2 ml of 4 M hydrogen chloride in ethyl acetate or 50% trifluoroacetic acid in methylene chloride and stirred at a temperature of from ice-cooling to room temperature for a period of from 1 to 4 hours. By evaporating the solvent, from 10 to 50 mg of respective N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl)amide or sulfonamide derivatives were obtained as hydrochloride or trifluoroacetate.

[0103] Their purity was verified by a liquid chromatography, and products having low purity were subjected to a liquid chromatography (methanol/5 mM trifluoroacetic acid aqueous solution). At the time of elution from the column, mass spectrometry was simultaneously carried out and only the eluates containing compounds having desired molecular weights were collected. After evaporating the solvent, compounds of interest having improved purity were obtained.

<Synthesis examples of compounds: a-1>

[0104] A pyridine (1.0 ml) solution of tert-butyl (4-{4-[2-(4-methoxyphenylaminoacetylamino)phenyl]thiazol-2-yl}carbamate (13.8 mg) was mixed with o-toluoyl chloride (10 μl) and stirred at 60°C for 1.5 hours. By adding 33 mg of PS-Tris Amine (carrying amount 4.61 mmol/g) and stirring at room temperature for 3 hours, excess amounts of o-toluoyl chloride and chloride ions were captured. The PS-Tris Amine was removed by filtration, and pyridine was evaporated under a reduced pressure from the filtered solution. A 16.4 mg portion of N-({[4-(2-tert-butoxycarbonylaminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl)-4-methylbenzamide hardly containing pyridine salt was obtained. This was mixed with 4 M hydrogen chloride in ethyl acetate (1.0 ml) and stirred at room temperature for 2.5 hours. By evaporating the solvent, 17.5 mg of N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl)-4-methylbenzamide hydrochloride was obtained.

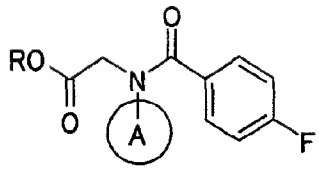
[0105] In the same manner, the compounds of a-2 to a-28 shown in the flowing Table 19 and the compounds of b-1 to b-70 shown in the flowing Tables 20 and 21 were obtained as hydrochloride or trifluoroacetate.

[0106] Physicochemical properties of the reference example compounds are shown in Tables 2 to 7, and structures and physicochemical properties of the Example compounds in Tables 8 to 21. Also, other compounds to be included in the invention are illustratively shown in Tables 22 to 25. These compounds can be easily produced in the same manner as the methods described in the aforementioned examples or the production methods, or by applying thereto slight modifications obvious to those skilled in the art.

[0107] Abbreviations in the tables respectively means Ref: Reference Example; Ex: Example; Co: compound number; Str: structural formula; Sal: salt; Dat: physicochemical properties {F: FAB-MS (M^+); F+: FAB-MS [$(M+H)^+$]; F-: FAB-MS [$(M-H)^-$]; A+: APCI (atmosphere chemical ionization)-MS [$(M+H)^+$]; E+: ESI (electrospray ionization)-MS [$(M+H)^+$]; N1: characteristic peak δ ppm of ^{1}H-NMR (DMSO-d_6, TMS internal standard); N2: characteristic peak δ ppm of ^{1}H-NMR ($CDCl_3$, TMS internal standard)}; Ph: phenyl; Pr: n-propyl; iPr: isopropyl; Ac: acetyl; Bn: benzyl; tBu: tert-butyl; iBu: isobutyl; Bu: n-butyl; cBu: cyclobutyl; Py2: 2-pyridyl; Py3: 3-pyridyl; Py4: 4-pyridyl; Th2: 2-thienyl; Th3: 3-thienyl; Fu: 2-furyl; Pyr: 2-pyrazinyl; Naph1: 1-naphthyl; Naph2: 2-naphthyl; cPen: cyclopentyl; cHex: cyclohexyl; Hep4: 4-heptyl; Pipe: 4-piperidinyl; Pyrr: 2-pyrrolyl; Pyra: 3-pyrazolyl; Ind3: 3-indolyl; and Ind5: 5-indolyl. In this connection, the numeral before each substituent group indicates its substitution position, for example, 3,4-Cl_2-5-F-Ph

indicates 3,4-dichloro-5-fluorophenyl group.

Table 2



(IIIa)

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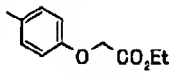
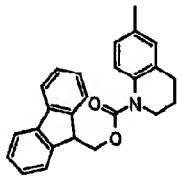
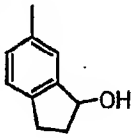
1	Ph	Et	F+: 302	2		Bn	F+: 466
3		Bn	F+:640	4		Et	F+:358
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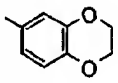
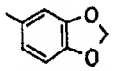
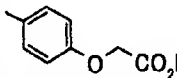
17	4-Br-Ph	Et	F+: 380	18	2-F-Ph	Et	F+: 320
19	3-F-Ph	Et	F+: 320	20	3,4-F_2-Ph	Et	F+: 338
21	4-SMe-Ph	Et	F+: 348	22	4-CO_2Et-Ph	Et	F+: 374
23	4-Me-Ph	Et	F+: 316	24	4-CF_3-Ph	Et	F+: 370
25	4-Et-Ph	Et	F+: 330	26	4-$N(Me)_2$-Ph	H	F+: 317
27	2-OMe-Ph	Et	F+: 332	28	3-OMe-Ph	Et	F+: 332
29	4-OMe-Ph	Et	F+: 332	30	3,4-$(OMe)_2$-Ph	Et	F: 361
31	3,4,5-$(OMe)_3$-Ph	Et	F: 391	32	4-OEt-Ph	Et	F+: 346
33	4-OPr-Ph	Et	F+: 360	34	4-OiPr-Ph	Et	F+: 360
35	4-OAc-Ph	Et	F+: 360	36		Et	F+: 360
37		Et	F: 345	38		Bn	F+: 466
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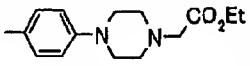
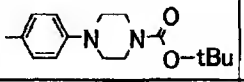
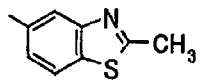
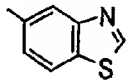
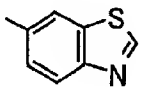
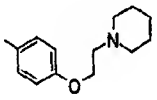
41		Bn	F: 533	42		Et	F: 485
43		Et	F+: 373	44		Et	F+: 359
45		Et	F+: 359	46		Et	F+: 429

Table 3

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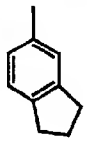
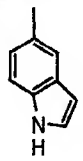
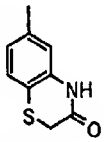
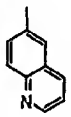
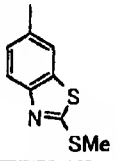
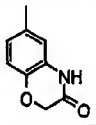
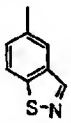
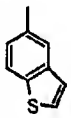
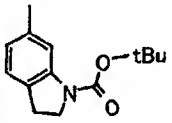
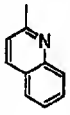
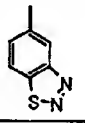
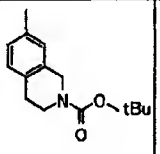
47		Et	F+:342	48		Et	F+:341
49		Et	F+:389	50		Et	F+:353
51		Et	F+:405	52		Et	F+:342
53		Et	F+:373	54		Et	F+:359
55		Et	F+:358	56		Et	F+:443
57		Et	F+:353	58		Et	F+:360
59		Et	F+:457				

Table 4

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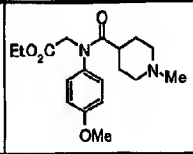
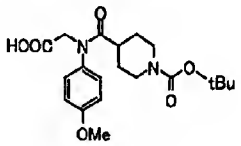
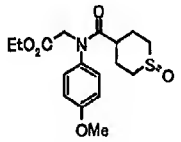
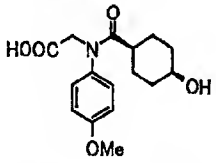
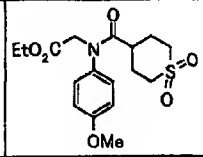
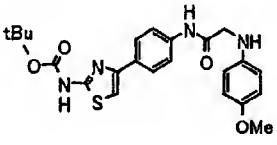
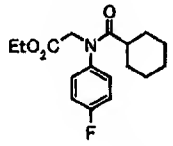
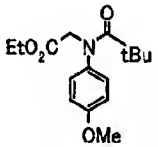
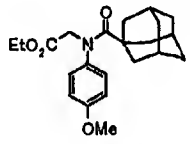
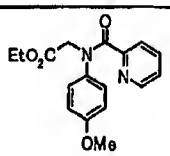
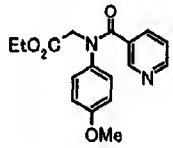
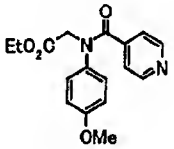
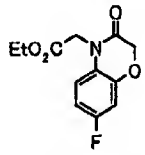
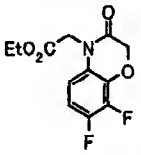
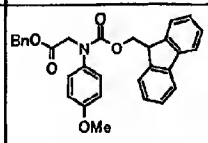
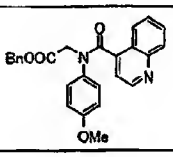
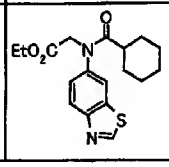
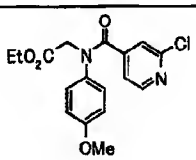
6		F+:335	7		F+:393
8		F+: 354	9		F-:306
10		F+: 370	11		F: 454
60		F+: 308	61		F+: 294
62		F-: 370	63		F+: 315
64		F+: 315	65		F+: 315
66		F: 253	67		F: 271
68		F: 493	69		F+:427
70		F+:347	71		F+:349

Table 5

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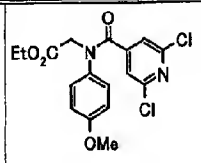
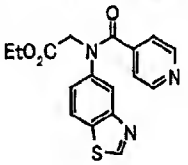
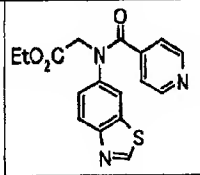
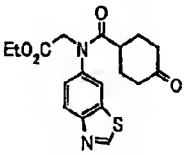
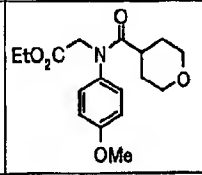
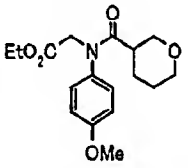
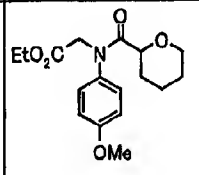
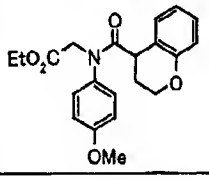
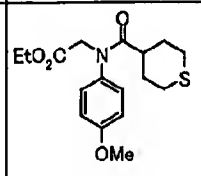
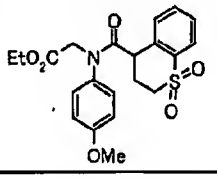
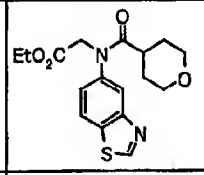
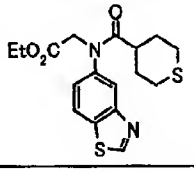
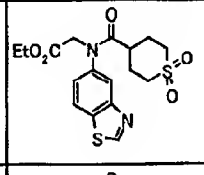
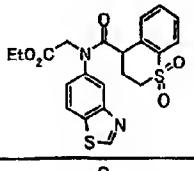
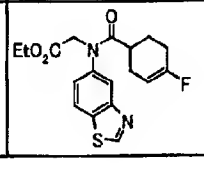
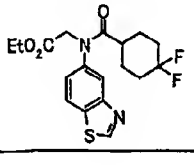
72		F:383	73		F+:342
74		F+:342	75		F-:331
76		F+: 322	77		F+: 322
78		F+: 322	79		F+: 370
80		F+: 338	81		F+: 418
82		F+: 349	83		F+: 365
84		F+: 397	85		F+: 445
86		F+:363	87		F+:383

Table 6

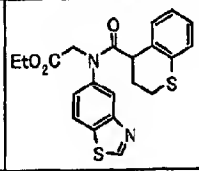
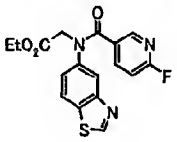
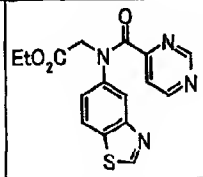
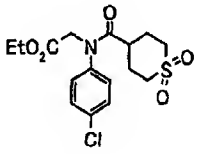
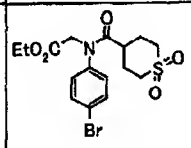
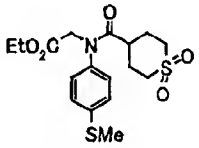
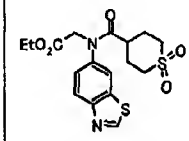
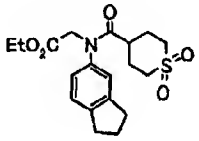
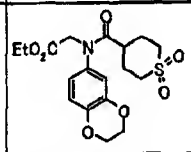
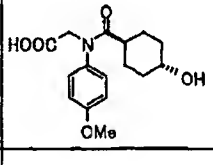
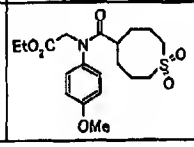
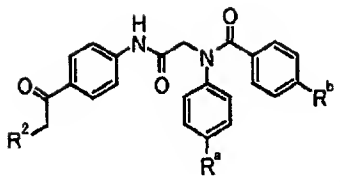
Ref	Str	Dat	Ref	Str	Dat
88		F+: 413	89		F+: 360
90		F+: 343	91		F+: 374
92		F+: 418	93		F+: 386
94		F+: 397	95		F+: 380
96		F+: 398	97		F+:308
98		F+: 398			

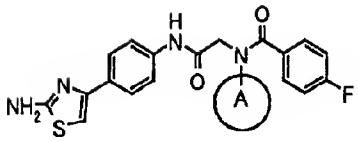
Table 7



(XV)

Ref	R^2	R^a	R^b	Dat	Ref	R^2	R^a	R^b	Dat
12	H	F	F	F+: 409	13	H	F	$CONH_2$	F-: 444
99	H	OMe	CO_2Me	F+: 461	100	CO_2Et	F	F	F-: 479

Table 8



(I)

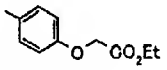
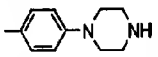
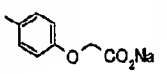
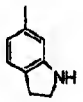
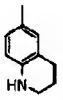
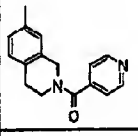
Ex	A	Sal	Dat
1	Ph	HCl	N1: 4.67(2H, s), 7.01-7.40(10H, m), 7.69-7.77(4H, m), 10.50(1H, s)
2	4-SOMe-Ph	HCl	F+: 509
3	4-CO_2Et-Ph	HCl	F+: 519
4		HCl	N1: 1.17(3H, t), 4.13(2H, q), 4.62(2H, s), 4.72(2H, s), 6.83(2H, d), 7.08(2H, m), 7.13(1H, s), 7.17(2H, d), 7.33(2H, m), 7.73(4H, m), 10.51(1H, s)
5		3HCl	N1: 3.15(4H, br), 3.32(4H, br), 4.61(2H, s), 6.87(2H, d), 7.07-7.15(5H, m), 7.34(2H, br), 7.74(4H, br), 10.58(1H, s)
6		–	N1: 4.07(2H s), 4.56(2H, s), 6.69(2H, d), 6.89(1H, s), 7.03-7.09(6H, m), 7.33(2H, br), 7.62(2H d), 7.73(2H, d), 10.52(1H, s)
7		2HCl	F+: 488 N1: 3.08(2H, t), 3.63(2H, t), 4.65(2H, s), 7.06-7.32(6H, m), 7.33-7.45(2H, m), 7.71-7.79(4H, m), 10.66(1H, s)
8		2HCl	F+: 502 N1: 1.88(2H, m), 2.68(2H, m), 3.24(2H, m), 4.63(2H, s), 6.91(1H, m), 6.98(1H, m), 7.10-7.15(4H, m), 7.39(2H, m), 7.74(4H, br), 10.58(1H, s)
9		2HCl	F+: 607
19	4-F-Ph	HCl	F+: 465 N1: 4.66(2H, s), 7.07-7.14(5H, m), 7.28-7.36(4H, m), 7.74(4H, m), 10.55(1H, s)
20	4-Cl-Ph	HCl	F+: 481
21	4-Br-Ph	HCl	F+: 527 N1: 4.67(2H, s), 7.09-7.21(5H, m), 7.32-7.40(2H, m), 7.44-7.51(2H, m), 7.69-7.76(4H, m), 10.56(1H, s)
22	2-F-Ph	HCl	N1: 4.10-5.17(2H, m), 7.05-7.55(9H, m), 7.69-7.78(4H, m), 10.58(1H, s)
23	3-F-Ph	HCl	N1: 4.69(2H, s), 7.00-7.22(6H, m), 7.24-7.44(3H, m),7.71-7.78(4H, m), 10.58(1H, s)

Table 9

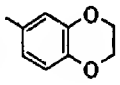
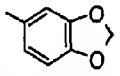
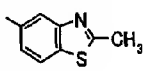
Ex	A	Sal	Dat
24	3,4-F_2-Ph	HCl	N1: 4.67(2H, s), 7.04-7.18(4H, m), 7.30-7.49(4H, m), 7.70-7.76(4H, m), 10.56(1H, s)
25	4-SMe-Ph	HCl	F+: 493 N1: 2.41(3H, s), 4.64(2H, s), 7.07-7.22(7H, m), 7.32-7.40(2H, m),7.69-7.77(4H, m), 10.54(1H, s)
26	4-Me-Ph	HCl	N1: 2.22(3H, s), 4.62(2H, s), 7.04-7.14(7H, m), 7.30-7.38(2H, m), 7.67-7.75(4H, m), 10.39(1H, s)
27	4-Et-Ph	HCl	F+: 475
28	4-CF_3-Ph	HCl	N1: 4.74(2H, s), 7.09-7.13(3H, m), 7.35-7.45(4H, m), 7.63-7.76(6H, m), 10.56(1H, s)
29	4-$N(Me)_2$-Ph	–	F-: 488
30	2-OMe-Ph	HCl	F+: 477
31	3-OMe-Ph	HCl	F+: 477
32	4-OMe-Ph	HCl	F+: 477 N1: 3.69(3H, s), 4.61(2H, s), 6.79-6.86(2H, m), 7.04-7.21(5H, m), 7.28-7.39(2H, m), 7.69-7.75(4H, m), 10.45(1H, s)
33	3,4-$(OMe)_2$-Ph	HCl	F+: 507 N1: 3.62(3H, s), 3.68(3H, s), 4.63(2H, s), 6.68-6.83(2H, m), 6.88-6.93(1H, m), 7.05-7.15(3H, m), 7.30-7.42(2H, m), 7.70-7.77(4H, m), 10.50(1H, s)
34	3,4,5-$(OMe)_3$-Ph	HCl	F+: 537
35	4-OEt-Ph	HCl	F+: 491
36	4-OPr-Ph	HCl	F+: 505
37	4-OiPr-Ph	HCl	F+: 505
38	4-OH-Ph	HCl	F+: 463 N1: 4.59(2H, s), 6.64(2H, d), 7.03-7.10(4H, m), 7.12(1H,s), 7.30-7.33(2H, m), 7.69-7.75(4H, m), 8.71(1H, brs), 9.55(1H, brs), 10.46(1H, s)
39		HCl	F+: 505 N1: 4.15-4.21(4H, m), 4.58(2H, s), 6.65-6.76(2H, m), 6.81(1H, d), 7.07-7.16(3H, m), 7.32-7.42(2H, m), 7.69-7.75(4H, m), 10.47(1H, s)
40		HCl	F+: 491 N1: 4.59(2H, s), 6.00(2H, s), 6.67-6.82(2H, m), 6.91(1H, d), 7.07-7.17(3H, m), 7.33-7.42(2H, m), 7.68-7.75(4H, m), 10.44(1H, s)
41	4-CH_2CN-Ph	HCl	F+: 486
42		2HCl	F+: 518 N1: 2.76(3H, s), 4.75(2H, s), 7.03-7.11(2H, m), 7.15(1H, s), 7.25-7.32(1H, m), 7.35-7.43(2H, m), 7.70-7.81(5H, m), 7.92(1H, d), 10.59(1H, s)

Table 10

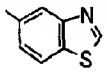
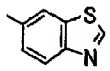
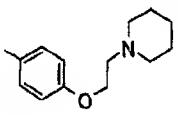
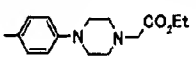
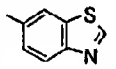
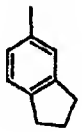
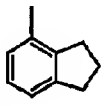
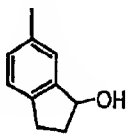
Ex	A	Sal	Dat
43		HCl	F+: 504 N1: 4.76(2H, s), 7.04-7.12(3H, m), 7.33-7.44(3H, m), 7.68-7.75(4H, m), 8.00(1H, d), 8.05(1H, d), 9.40(1H, s), 10.47(1H, s)
44		–	F-: 502 N1: 4.73(2H, s), 6.90(1H, s), 7.01-7.12(4H, m), 7.35-7.43(3H, m), 7.59(2H, d), 7.75(2H, d), 7.97(1H, d), 8.10(1H, d), 9.37(1H, s), 10.26(1H, s)
45		2HCl	N1: 1.34-1.37(1H, m), 1.65-1.69(1H, m), 1.75-1.84(4H, m), 2.91-3.00(2H, m), 3.39-3.46(4H, m), 4.34(2H, t), 4.62(2H, s), 6.89(2H, d), 7.08(2H, d), 7.12(1H, s), 7.20(2H, d), 7.35(2H, br), 7.71-7.76(4H, m), 8.74(1H, br), 10.57(2H, br)
46	Th3	HCl	N1: 4.60(2H, s), 6.88-7.01(1H, m), 7.09(1H, s), 7.10-7.16(2H, m), 7.22-7.25(1H, m), 7.35-7.44(3H, m), 7.69-7.73(4H, m), 10.42(1H, s)
47	4-CH_2COOEt-Ph	HCl	F+: 533
48		2HCl	N1: 1.25(3H, t), 3.0-3.5(8H, m), 4.24(2H, q), 4.30(2H, s), 4.61(2H, s), 6.88(2H, d), 7.07-7.13(5H, m) 7.35(2H, m), 7.70-7.76(4H m), 10.55(1H, s)
49		HCl	F+: 504 N1: 4.76(2H, s), 7.07(2H, t), 7.13(1H, s), 7.37-7.42(3H, m), 7.74(4H, brs), 7.97(1H, d), 8.10(1H, d), 9.37(1H, s), 10.56(1H, s)
50		HCl	F+: 487 N1: 1.90-2.02(2H, m), 2.72-2.81(4H, m), 4.63(2H, s), 6.92(1H, d), 7.05-7.16(5H, m), 7.32-7.41(2H, m), 7.71-7.76(4H, m), 10.53(1H, s)
51		HCl	F+: 487
52		–	F+: 503 N1: 1.66-1.80(1H, m), 2.25-2.36(1H, m), 2.57-2.69(1H, m), 2.76-2.87(1H, m), 4.56(1H, d), 4.63(1H, d), 4.90-4.98(1H, d), 5.26(1H, d), 6.90(1H, s), 6.97-7.13(6H, m), 7.25(1H, br), 7.32-7.43(2H, m), 7.61(2H, d), 7.74(2H, d), 10.20(1H, s)

Table 11

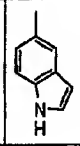
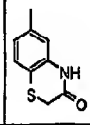
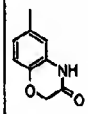
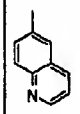
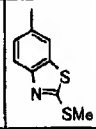
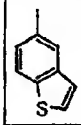
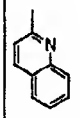
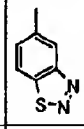
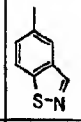
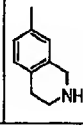
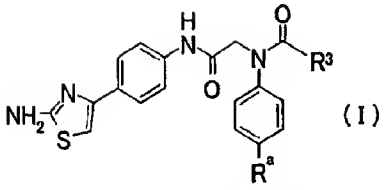
Ex	A	Sal	Dat
53		–	F+: 486 N1: 4.63(2H, s), 6.36(1H, s), 6.90(1H, s), 6.96-7.05(5H, m), 7.26(1H, d), 7.31-7.39(3H,m), 7.44(1H, s), 7.61(2H, d), 7.74(2H, d), 10.16(1H, s), 11.13(1H, s)
54		HCl	F+: 534 N1: 3.42(2H, s), 4.61(2H, s), 6.79-6.84(1H, m), 6.89(1H , d), 7.09-7.24(4H, m), 7.34-7.43(2H, m), 7.68-7.76(4 H, m), 10.48(1H, s), 10.53(1H, s)
55		HCl	F+:518 N1: 4.53(2H, S), 4.56(2H, s), 6.77-6.85(3H, m), 7.04-7. 15(3H, m), 7.37(2H, br), 7.72(4H, m), 10.25(1H, S), 10.68(1H, S)
56		2HCl	F+: 498 N1: 4.87(2H, s), 7.10(2H, t), 7.16(1H, s), 7.40-7.48(2H, m), 7.70-7.81(4H, m), 7.82-7.91(2H, m), 8.11-8.21(2 H, m), 8.84(1H, d), 9.13(1H, d), 10.77(1H, s)
57		HCl	F+: 550 N1: 2.76(3H, s), 4.72(2H, s), 7.03-7.13(3H, m), 7.28-7. 40(3H, m), 7.69-7.76(5H, m), 7.94(1H, d), 10.51(1H, s)
58		HCl	F+:503 N1: 4.72(2H, s), 7.06(2H, t), 7.11(1H, s), 7.24(1H, dd), 7.36-7.40(3H, m), 7.73(4H, br), 7.76-7.79(2H, m), 7. 90(2H, d), 10.49(1H, s)
59	Py2	HCl	F+: 448 N1: 4.85(2H, s), 7.01(1H, d), 7.12-7.21(4H, m), 7.38-7. 46(2H, m), 7.62-7.68(1H, m), 7.70-7.77(4H, m), 8.38(1H, d), 10.68(1H, s)
60		–	F+: 498 N1: 4.98(2H, s), 6.90(1H, s), 7.02(2H, br), 7.13-7.26(3 H, m), 7.50-7.63(5H, m), 7.68-7.77(4H, m), 7.88(1H, d), 8.16(1H, d), 10.34(1H, s)
61		HCl	F+: 505 N1: 4.88(2H, s), 7.09(2H, t), 7.16(1H, s), 7.41-7.50(2H, m), 7.64-7.71(1H, m), 7.73-7.82(4H, m), 8.30(1H, d), 8.63(1H, d), 10.72(1H, s)
62		HCl	F+: 504 N1: 4.75(2H, s), 7.05-7.15(3H, m), 7.34-7.48(3H, m), 7. 66-7.81(6H, m), 9.71(1H, s), 10.61(1H, s)
63		2HCl	F+: 502 N1: 2.88-2.97(2H, m), 3.24-3.36(2H, m), 4.10-4.19(2H, m), 4.65(2H, s), 7.03-7.21(6H, m), 7.35-7.44(2H, m), 7.70-7.78(4H, m), 10.64(1H, s)

Table 12



(I)

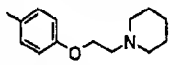
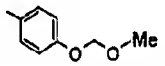
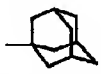
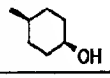
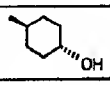
Ex	R^a	R^3	Sal	Dat
10	OMe	4-$CONH_2$-Ph	HCl	F+: 503
11	OMe	4-COONa-Ph	–	F+: 525
12	OMe	4-OH-Ph	HCl	N1: 3.70(3H, s) 4.57(2H, s), 6.59(2H, d), 6.82(2H d), 7.12-7.15(5H, m), 7.72(4H br), 10.44(1H, s)
13	OMe	Pipe	2HCl	F+: 466
64	F	cHex	HCl	F+: 453
65	OMe	Py2	2HCl	F+: 460
66	OMe	Py3	–	F-: 458
67	OMe	Py4	2HCl	F+: 460 N1: 3.68(3H, s), 4.71(2H, s), 6.83(2H, d), 7.18(1H, s), 7.28(2H, d), 7.66-7.82(6H, m), 8.74(2H, d), 10.80(1H, s)
68	OMe	4-COOMe-Ph	HCl	F+:517
69	OMe		2HCl	F+: 586
70	OMe		HCl	F+: 519
71	OMe	tBu	HCl	N1: 0.98(9H, s), 3.77(3H, s), 4.25(2H, s), 6.94-7.00(2H, m), 7.11(1H, s), 7.39-7.45(2H, m), 7.66-7.74(4H, m), 10.27(1H, s)
72	OMe		HCl	N1: 1.38-1.47(3H, m), 1.49-1.58(3H, m), 1.66-1.73(6H, m), 1.77-1.83(3H, m), 6.98(2H, d), 7.10(1H, s), 7.40(2H d), 7.66-7.74(4H, m), 10.24(1H, s)
73	OMe		HCl	F+: 481
74	OMe		HCl	F+: 481

Table 13

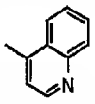
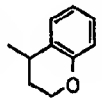
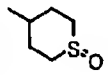
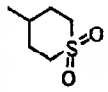
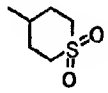
Ex	R^a	R^3	Sal	Dat
75	OMe	1-Me-Pipe	2HCl	F+: 480
76	OMe		–	N1: 3.32(3H, s), 4.70(2H, s), 6.64(2H, d), 6.92(1 H, s), 7.03(2H, br), 7.25'2H, d), 7.41(1H, d), 7. 65-7.79(6H, m), 7.95(1H, d), 8.33(1H, d), 8.77(1H, d), 10.30(1H, s)
77	OMe	2,6-Cl_2-Py4	HCl	N1: 3.70(3H, s), 4.65(2H, s), 6.88(2H, d), 7.13(1 H, d), 7.30(2H, d), 7.42(2H, s), 7.74(4H, m), 1 0.57(1H, s)
78	OMe	2-Cl-Py4	HCl	F+:494
79	OMe		HCl	N1: 1.46-1.49(2H, m), 1.56-1.66(2H, m), 2.5(1H, m), 3.02-3.07(2H, m), 3.74-3.78(5H, m), 4.35(2 H, s), 6.99-7.02(2H, m), 7.09(1H, s), 7.39-7.41(2H, m), 7.66-7.72(4H, m), 10.30(1H, s)
80	OMe		HCl	F+: 467
81	OMe		HCl	F+: 467
82	OMe		HCl	N1: 1.93-2.10(2H, m), 3.78-3.86(4H, m), 3.93-3.9 8(1H, m), 4.25-4.30(1H, m), 4.38(1H, d), 4.52(1H, d), 6.71(1H, d), 6.82-6.85(1H, m), 7.04-7.1 6(5H, m), 7.57(2H, d), 7.68-7.74(4H, m), 10.39 (1H, s)
83	OMe		HCl	F+: 483 N1: 1.62-1.70(2H, m), 1.90-1.93(2H, m), 2.30-2.3 7(3H, m), 2.53-2.54(2H, m), 3.78(3H, s), 4.33(2 H, s), 7.00(2H, d), 7.09(1H, s), 7.38(2H, d), 7. 66-7.72(4H, m), 10.30(1H, s)
84	OMe		HCl	F+: 499
85	OMe		HCl	F+: 515 N1: 2.00-2.08(4H, m), 2.63-2.70(1H, m), 2.93-3.0 5(4H, m), 3.78(3H, s), 4.36(2H, s), 7.01(2H, d) , 7.11(1H, s), 7.40(2H, d), 7.67-7.73(4H, m), 1 0.37(1H, s)
86	Cl		HCl	F+: 519 N1: 2.0(4H, m), 2.68-2.73(1H, m), 3.00-3.02(4H, m), 4.40(2H, s), 7.12(1H, s), 7.50-7.56(4H, m), 7.68-7.74(4H, m), 10.44(1H, s)
87	OMe	4-OH-cHex	HCl	N1: 0.76-0.84(1H, m), 1.08-1.14(1H, m), 1.31-1.4 3(2H, m), 1.57-1.66(2H, m), 1.75-1.81(2H, m), 2. 1(1H, m), 2.2(1H, m), 3.3(1H, m), 3.7(1H, m), 4. 34(1H, s), 6.98-7.01(2H, m), 7.11(1H, s), 7.38(2 H, d), 7.67-7.73(4H, m), 10.33(1H, s)

Table 14

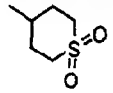
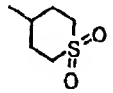
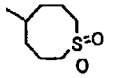
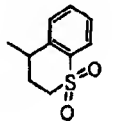
Ex	R^a	R^3	Sal	Dat
88	Br		HCl	F+: 563 N1: 1.96-2.10(4H, m), 2.65-2.76(1H, m),2.93-3.13(4H, m), 4.39(2H, s), 7.11(1H, s), 7.45(2H, d), 7.62-7.80(6H, m), 10.41(1H, s)
89	SMe		HCl	F+: 531 N1: 1.95-2.12(4H, m), 2.50(3H, s), 2.66-2.76(1H, m), 2.90-3.10(4H, m), 4.38(2H, s), 7.11(1H, s), 7.34(2H, d), 7.42(2H, d), 7.65-7.77(4H, m), 10.39(1H, s)
90	OMe		HCl	F+: 543 N1: 1.54-1.56(2H, m), 1.63-1.80(4H, m), 2.56-2.60(1H, m), 2.79-2.85(2H, m), 3.10-3.15(2H, m), 3.78(3H, s), 4.35(2H, 7.00-7.03(2H, m), 7.10(1H, s), 7.40-7.43(2H, m), 7.67-7.73(4H, m), 10.34(1H, m)
91	OMe		HCl	F+: 563 N1: 2.41-2.51(2H, m), 3.49-3.61(2H, m), 3.78(3H, s), 4.13(1H, t), 4.40(1H, d), 4.52(1H, d), 7.05-7.10(3H, m), , 7.47-7.53(2H, m), 7.58-7.64(3H, m), 7.68-7.78(5H, m), 10.42(1H, s)

Table 15

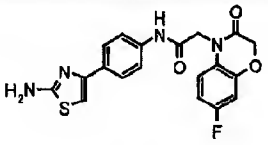
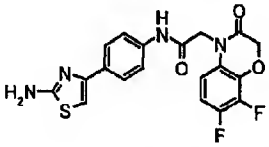
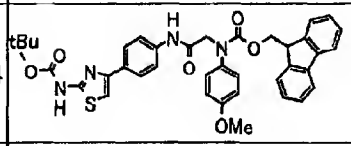
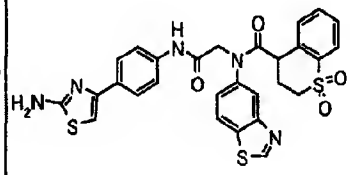
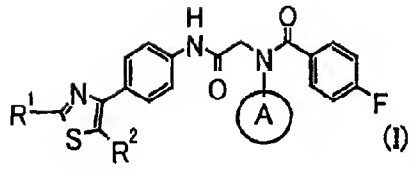
Ex	Str	Sal	Dat
92		HCl	N1: 4.76(2H, s), 4.79(2H, s), 6.90(1 H, dt), 7.00(1H, dd), 7.10-7.13(2H, m), 7.69(2H, d), 7.74(2H, d), 10. 70(1H, s)
93		HCl	N1: 4.81(2H, s), 4.88(2H, s), 6.94-6. 97(1H, m), 7.08-7.14(2H, m), 7.69 (2H, d), 7.74(2H, d), 10.73(1H, s)
94		—	F-: 675
95		—	F+: 590 N1: 2.47-2.59(2H, m), 3.48-3.60(2H, m), 4.18-4.21(1H, m), 4.50(1H, d) , 4.56(1H, d), 6.90(1H, s), 7.02(1 H, s), 7.49-7.53(1H, m), 7.57-7.66(4H, m), 7.73-7.77(3H, m), 7.82(1H , d), 8.33(1H, d), 8.43(1H, br), 9.5 0(1H, s), 10.19(1H, s)

Table 16



(I)

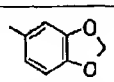
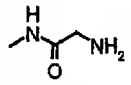
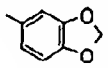
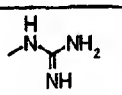
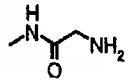
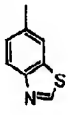
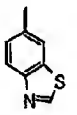
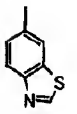
Ex	R^1	R^2	A	Sal	Dat
14	Me	H	4-F-Ph	—	F-: 462
15	NHAc	H		—	F+: 533
16		H		HCl	F+: 548
17	NH_2	Br	4-F-Ph	HCl	E: 543
96	CO_2Et	H	4-F-Ph	—	F+: 522
97	NH_2	CO_2Et	4-F-Ph	HCl	F: 356
98	NH-Me	H	4-F-Ph	HCl	F+: 479
99	NH-Ph	H	4-F-Ph	HBr	F+: 451
100	NH-Py2	H	4-F-Ph	2HCl	F+: 542
101		H	4-F-Ph	HCl	F+: 533
102		H	4-F-Ph	HCl	F+: 494
103		H	4-F-Ph	HCl	F+: 507
104		H		HCl	N1: 3.91(2H, s), 4.75(2H, s), 7.08(2H, t), 7.37-7.42(3H, m), 7.61(1H, s), 7.71(2H, d), 7.85(2H, d), 7.97(1H, d), 8.11(1H, d), 8.37(2H, br), 9.39(1H, s), 10.44(1H, s), 12.74(1H, s)
105	NHMe	H		HCl	N1: 3.00(3H, s), 4.75(2H, s), 7.05-7.09(3H, m), 7.36-7.42(3H, m), 7.71(1H, d), 7.76(1H, d), 7.97(1H, d), 8.11(1H, d), 9.37(1H, s), 10.50(1H, s)
106	NMe_2	H		HCl	F+:532

Table 17

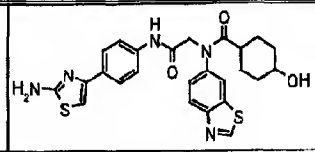
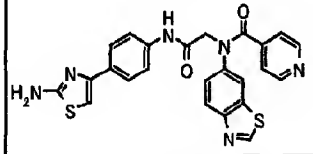
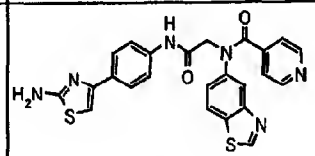
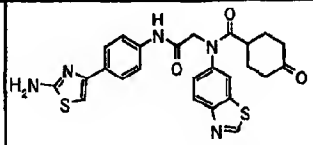
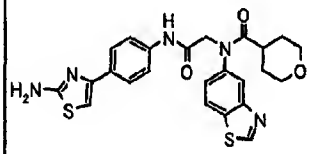
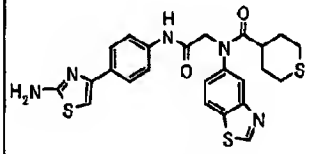
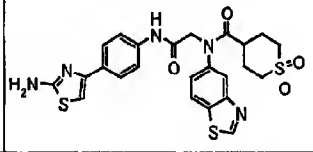
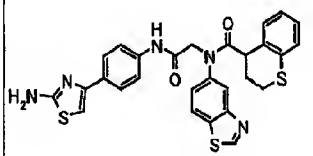
Ex	Str	Sal	Dat
18		HCl	F+: 508
107		2HCl	N1: 4.86(2H, s), 7.19(1H, s), 7.54(1 H, d), 7.76-7.87(6H, m), 7.99(1H, d), 8.75(2H, m), 9.41(1H, s), 10.9 0(1H, s)
108		2HCl	F+: 487 N1: 4.86(2H, s), 7.18(1H, s), 7.49(1 H, d), 7.78(6H, m), 8.09-8.13(2H, m), 8.71(2H, d), 9.43(1H, s), 10.8 3(1H, s)
109		–	F+: 506
110		HCl	F+: 494 N1: 1.51-1.54(2H, m), 1.60-1.70(2H, m), 2.53-2.56(1H, m), 2.98-3.04(2 H, m), 3.73-3.75(2H, m), 4.48(2H, s), 7.10(1H, d), 7.63(1H, d), 7.68 -7.73(4H, m), 8.23(1H, s), 8.27(1H , d), 9.49(1H, s), 10.37(1H, s)
111		HCl	F+: 510 N1: 1.65-1.74(2H, m), 1.97-2.00(2H, m), 2.28-2.48(5H, m), 4.47(s, 2H) , 7.11(1H, s), 7.61(1H, d), 7.69-7. 74(4H, m), 8.21(1H, s), 8.27(1H, d), 9.50(1H, s), 10.40(1H, s)
112		HCl	N1: 2.05-2.06(4H, m), 2.72-2.78(1H, m), 2.93-2.99(4H, m), 4.49(2H, s) , 7.11(1H, s), 7.63(1H, dd), 7.69-7 .74(4H, m), 8.23(1H, d), 8.28(1H, d), 9.50(1H, s), 10.42(1H, s)
113		HCl	F+: 558 N1: 2.07-2.18(2H, m), 2.84-2.90(1H, m), 3.09-3.15(1H, m), 3.83-3.86(1 H, m), 4.52(1H, d), 4.62(1H, d), 7 .01-7.10(4H, m), 7.30(1H, d), 7.72 -7.83(5H, m), 8.31(1H, d), 8.38(1H , d), 9.50(1H, s), 10.44(1H, s)

Table 18

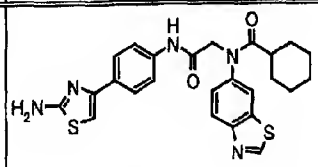
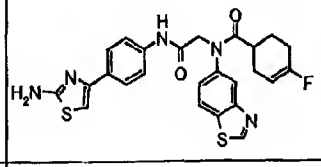
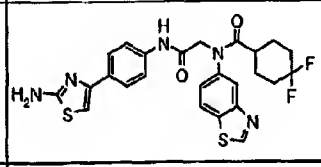
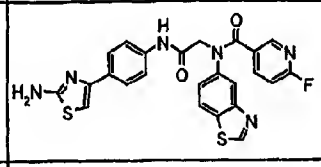
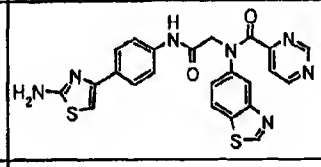
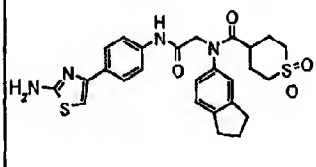
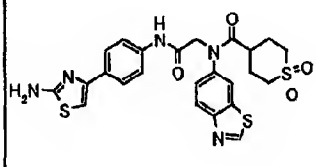
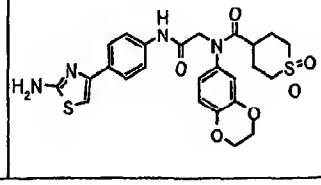
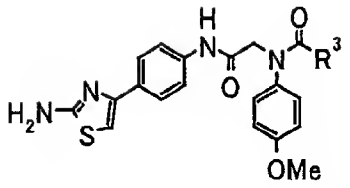
Ex	Str	Sal	Dat
114		HCl	F+:492 N1: 0.83-1.70(10H, m), 2.24(1H, m), 4.46(2H, s), 7.11(1H, s), 7.65(1H, d), 7.71(4H, m), 8.17(1H, d), 8.30(1H, s), 9.47(1H, s), 10.39(1H, s)
115		HCl	F+: 508 N1: 1.65-1.80(1H, m), 1.83-2.27(6H, m), 4.51(2H, m), 5.07-5.18(1H, m), 7.13(1H, m), 7.61-7.76(5H, m), 8.20-8.32(2H, m), 9.50(1H, s), 10.45(1H, s)
116		HCl	F+: 528 N1:1.44-2.02(8H, m), 2.40-2.60(1H, m), 4.49(2H, s), 7.11(1H, s), 7.59-7.78(5H, m), 8.19-8.34(2H, m), 9.49(1H, s), 10.40(1H, s)
117		HCl	F+: 505 N1: 4.80(2H, s), 7.08-7.12(2H, m), 7.44(1H, d), 7.73(4H, br), 7.9(1H, m), 8.05-8.19(3H, m), 9.43(1H, s), 10.56(1H, s),
118		HCl	F+: 488 N1: 4.82(2H, s), 7.16(1H, s), 7.42(1H, d), 7.63(1H, d), 7.75(4H, br), 8.03-8.06(2H, m), 8.79(1H, d), 8.98(1H, s), 9.40(1H, s), 10.66(1H, s)
119		HCl	F+: 525 N1: 1.95-2.15(6H, m), 2.67-2.78(1H, m), 2.79-3.13(6H, m), 4.37(2H, s), 7.13(1H, s), 7.18-7.23(1H, m), 7.27-7.34(2H, m), 7.68-7.78(4H, m), 10.42(1H, s)
120		HCl	F+: 542 N1: 2.05-2.06(4H, m), 2.70-2.77(1H, m), 3.0(4H, m), 4.48(2H, s), 7.14(1H, s), 7.67(1H, dd), 7.70-7.75(4H, m), 8.17(1H, d), 8.31(1H, d), 9.48(1H, s), 10.48(1H, s)
121		HCl	F+: 543 N1: 2.00-2.05(4H, m), 2.68-2.75(1H, m), 2.97-3.03(4H, m), 4.26(4H, br), 4.34(2H, s), 6.91-6.95(2H, m), 7.02(1H, d), 7.11(1H, s), 7.67-7.73(4H, m), 10.37(1H, s)

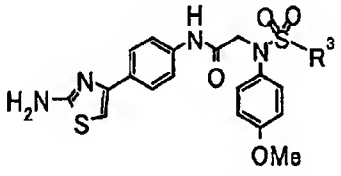
Table 19



(I)

Ex	R^3	Dat	Ex	R^3	Dat
a-1	2-Me-Ph	A+: 473	a-15	3,4-F_2-Ph	E+: 495
a-2	2,6-F_2-Ph	A+: 495	a-16	3-F-Ph	E+: 477
a-3	2,3-F_2-Ph	A+: 495	a-17	4-CO_2Me-Ph	E+: 515
a-4	2-Cl-Ph	A+: 493	a-18	2-OMe-Ph	E+: 489
a-5	2-CF_3-Ph	A+: 527	a-19	2-CO_2Me-Ph	E+: 517
a-6	Ph	E+: 459	a-20	4-Me-Ph	E+: 473
a-7	3-Me-Ph	E+: 473	a-21	3-CF_3-Ph	E+: 527
a-8	3-Br-Ph	E+: 538	a-22	3,4-Cl_2-Ph	E+: 528
a-9	3,5-Cl_2-Ph	E+: 528	a-23	2,4-Cl_2-Ph	E+: 528
a-10	2-F-Ph	E+: 477	a-24	Naph1	E+: 509
a-11	3-Cl-Ph	E+: 493	a-25	4-CF_3-Ph	E+: 527
a-12	3-OCF_3-Ph	E+: 543	a-26		E+: 515
a-13	3,5-F_2-Ph	E+: 495	a-27	Th2	E+: 465
a-14	2,4-F_2-Ph	E+: 495	a-28	Fu	E+: 449

Table 20



(I)

Ex	R^3	Dat	Ex	R^3	Dat
b-1	Ph	A+: 495	b-7	3-F-Ph	A+: 513
b-2	2,4-F_2-Ph	A+: 531	b-8	4-Cl-Ph	A+: 529
b-3	Me	A+: 433	b-9	3-Cl-Ph	A+: 529
b-4	Et	A+: 447	b-10	2-Cl-Ph	A+: 529
b-5	Pr	A+: 461	b-11	3-Me-Ph	A+: 509
b-6	iPr	A+: 461	b-12	4-Pr-Ph	A+: 537

Table 21

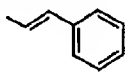
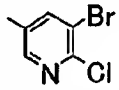
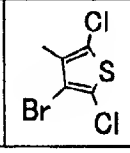
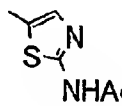
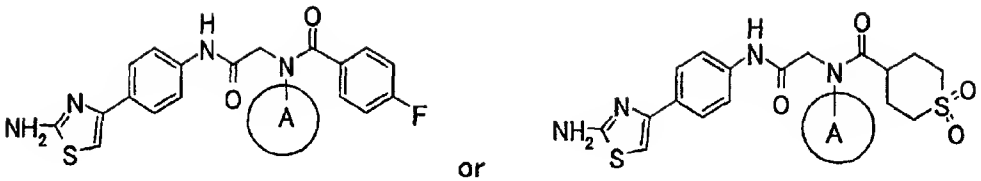
Ex	R^3	Dat	Ex	R^3	Dat
b-13	Bu	A+: 475	b-42	4-iPr-Ph	A+: 537
b-14	NMe_2	A+: 538	b-43	2,4,5-Cl_3-Ph	A+: 597
b-15	4-tBu-Ph	A+: 551	b-44	3,5-Cl_2-Ph	A+: 564
b-16	4-NHAc-Ph	A+: 552	b-45	3,4-Cl_2-Ph	A+: 564
b-17	4-OCF_3-Ph	A+: 579	b-46	2,5-Cl_2-Ph	A+: 564
b-18	4-Bu-Ph	A+: 567	b-47	2,6-Cl_2-Ph	A+: 564
b-19	3-CN-Ph	A+: 520	b-48	2,4-Cl_2-Ph	A+: 564
b-20	2-CN-Ph	A+: 520	b-49	2,3,4-Cl_3-Ph	A+: 597
b-21	4-CO_2H-Ph	A+: 539	b-50	2,3-Cl_2-Ph	A+: 564
b-22	3-CO_2H-Ph	A+: 539	b-51	3-Cl-2-Me-Ph	A+: 544
b-23	4-CF_3-Ph	A+: 563	b-52	3-Cl-2-F-Ph	A+: 548
b-24	3-CF_3-Ph	A+: 563	b-53	2-Cl-5-CF_3-Ph	A+: 598
b-25	2-CF_3-Ph	A+: 563	b-54	3,5-Cl_2-2-OH-Ph	A+: 580
b-26	4-NO_2-Ph	A+: 540	b-55	5-Cl-2-OMe-Ph	A+: 560
b-27	3-NO_2-Ph	A+: 540	b-56	2-Cl-4-CN-Ph	A+: 555
b-28	2-NO_2-Ph	A+: 540	b-57	4-Cl-3-NO_2-Ph	A+: 575
b-29	4-Br-Ph	A+: 573	b-58	4-Br-2-Et-Ph	A+: 602
b-30	2-Br-Ph	A+: 573	b-59	2,5-Br_2-3,6-F_2-Ph	A+: 689
b-31	4-F-Ph	A+: 513	b-60	4-Br-2,5-F_2-Ph	A+: 610
b-32		A+: 521	b-61		A+: 609
b-33	2,5-Br_2-Ph	A+: 652	b-62	5-Br-2-OMe-Ph	A+: 604
b-34	5-F-2-Me-Ph	A+: 527	b-63	4-CO_2Me-3-OMe-Th2	A+: 589
b-35	3,5-$(CF_3)_2$-Ph	A+: 631	b-64	5-Pyr-Th2	A+: 578
b-36	4-OMe-2-NO_2-Ph	A+: 570	b-65	3-Br-5-Cl-Th2	A+: 613
b-37	2,5-$(Me)_2$-Ph	A+: 523	b-66	5-Cl-Th2	A+: 536
b-38	2-OMe-4-Me-Ph	A+: 539	b-67	Th2	A+: 501
b-39	2,5-$(OMe)_2$-Ph	A+: 555	b-68	2,3,5,6-$(Me)_4$-Ph	A+: 551
b-40	Naph1	A+: 545	b-69	4-Ph-Ph	A+: 571
b-41		A+: 649	b-70		A+: 573

Table 22



or

(I)

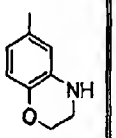
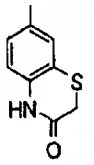
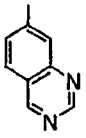
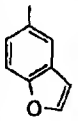
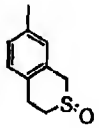
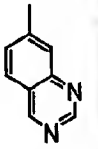
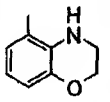
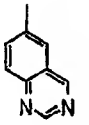
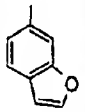
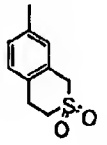
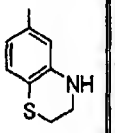
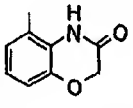
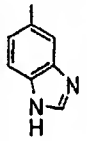
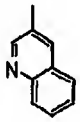
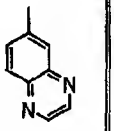
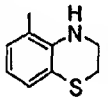
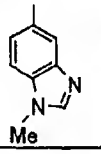
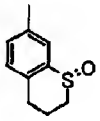
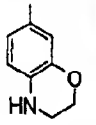
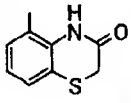
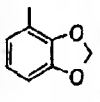
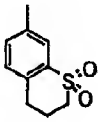
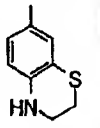
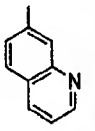
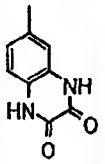
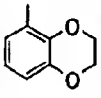
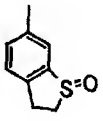
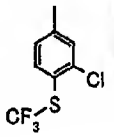
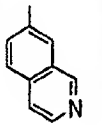
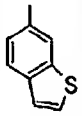
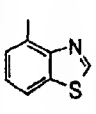
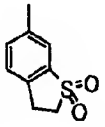
Co	A	Co	A	Co	A	Co	A	Co	A
1		8		15		22		29	
2		9		16		23		30	
3		10		17		24		31	
4		11		18		25		32	
5		12		19		26		33	
6		13		20		27		34	
7		14		21		28		35	

Table 23

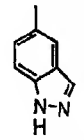
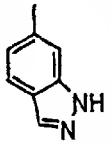
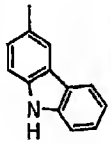
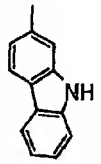
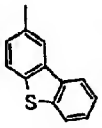
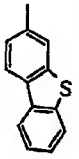
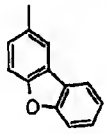
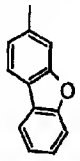
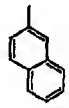
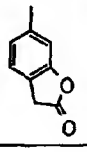
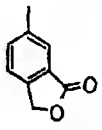
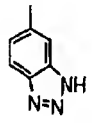
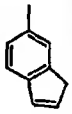
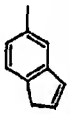
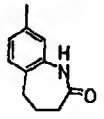
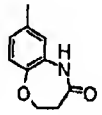
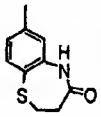
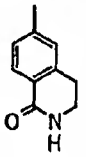
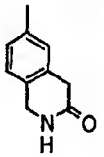
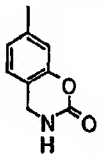
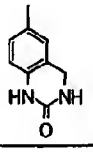
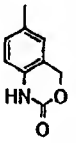
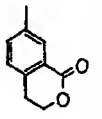
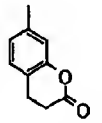
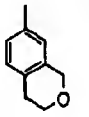
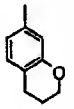
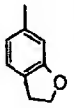
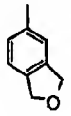
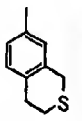
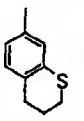
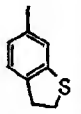
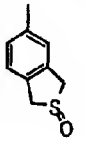
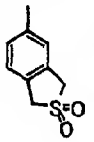
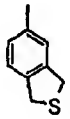
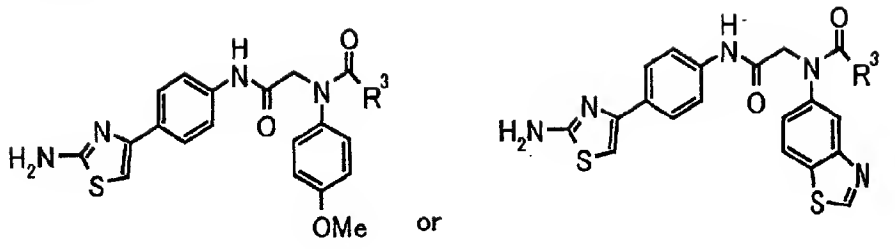
Co	A	Co	A	Co	A	Co	A
36		45		54		63	
37		46		55		64	
38		47		56		65	
39		48		57		66	
40		49		58		67	
41		50		59		68	
42		51		60		69	
43		52		61			
44		53		62			

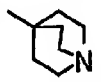
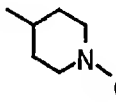
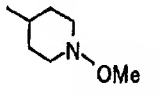
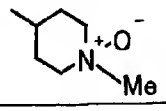
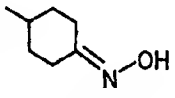
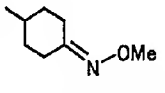
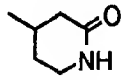
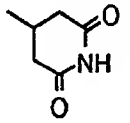
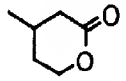
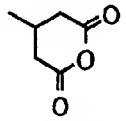
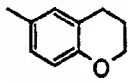
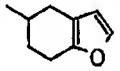
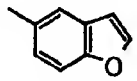
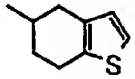
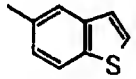
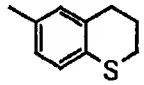
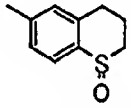
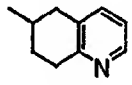
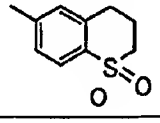
Table 24



(I)

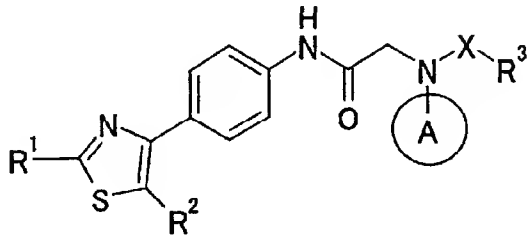
Co	R^3	Co	R^3	Co	R^3
70	2-Cl-4-NO_2-Ph	103	3,5-$(OMe)_2$-Ph	136	Py2
71	CH_2(4-Cl-Ph)	104	2-COPh-Ph	137	Py4
72	2-OAc-Ph	105	$CH_2CH_2CO_2Me$	138	Py3
73	3-CN-Ph	106	$CH=CHCO_2Et$	139	NO_2-Ph
74	2,5-F_2-Ph	107	$CH(cHex)_2$	140	Me
75	4-OMe-Ph	108	2-OMe-Ac	141	Et
76	4-NO_2-Ph	109	$CH_2CH_2CH_2CO_2Me$	142	iPr
77	2,6-F_2-Ph	110	$CH_2CH_2CH_2Ph$	143	tBu
78	2,3,4,5,6-F_5-Ph	111	$COCH_2Ph$	144	iBu
79	3,4-$(OMe)_2$-Ph	112	CH_2(3-NO_2-Ph)	145	Hep4
80	4-CN-Ph	113	CH_2(2-Cl-Ph)	146	cBu
81	2-NO_2-Ph	114	CH_2(2-F-Ph)	147	cHex
82	4-Br-Ph	115	CH_2(2-Me-Ph)	148	cPen
83	OCH_2(4-NO_2-Ph)	116	CH_2(2-OMe-Ph)	149	CCl_3
84	4-OMe-cHex	117	CH_2(Naph1)	150	Naph2
85	2-NHAc-Ph	118	CH_2(3,4-$(OMe)_2$-Ph)	151	4-Ph-Ph
86	4-Br-2-Me-Ph	119	CH_2(3,4,5-$(OMe)_3$-Ph)	152	2-F-Ph
87	3-Br-4-Me-Ph	120	CH_2-cHex	153	2-Br-Ph
88	4-Cl-3-NO_2-Ph	121	CH_2 (2-NO_2-Ph)	154	$CH(Ph)_2$
89	5-CO_2H-2-F-Ph	122	CH_2(4-NO_2-Ph)	155	4-Me-Ph
90	3-Cl-4-Me-Ph	123	CH_2(3-Cl-Ph)	156	2-CO_2Me-Ph
91	2,4,6-$(OMe)_3$-Ph	124	CH_2(2-Br-Ph)	157	4-CO_2Me-Ph
92	2-Ac-Ph	125	CH_2(3-Me-Ph)	158	5-Cl-Th2
93	3-NMe_2-Ph	126	CH_2(3-OMe-Ph)	159	3-Me-Th2
94	3-OPh-Ph	127	CH_2(Th3)	160	1-Me-Pyrr
95	2-Br-5-OMe-Ph	128	CH_2(Naph2)	161	Fu
96	4-CO_2H-2-Me-Ph	129	CH_2(2,4-Cl-Ph)	162	Pyra
97	3-OMe-2-NO_2-Ph	130	4-Cl-Ph	163	Ind5
98	2-CO_2H-4-Cl-Ph	131	3-OMe-Ph	164	4-Bu-Ph
99	3-OMe-4-Me-Ph	132	3-CO_2Me-Ph	165	2-OPh-Ac
100	Th3	133	4-iPr-Ph	166	3-CF_3-Ph
101	5-Br-Th2	134	5-NO_2-Fu	167	4-Ac-Ph
102	Pyrr	135	6-Me-Py2	168	Ind3

Table 25

Co	R^3	Co	R^3	Co	R^3
169		176		183	
170		177		184	
171		178		185	
172		179		186	
173		180		187	
174		181			
175		182			

Claims

1. An amide derivative represented by the following general formula (I) or a salt thereof



(I)

(symbols in the formula have the following meanings;

R^1 and R^2: the same or different from each other, and each represents -H, -lower alkyl, -lower alkenyl, -lower alkynyl, -cycloalkyl, -cycloalkenyl, -NRaRb, -NRc-NRaRb, -NRc-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -NRc-C(=NH)-NRaRb, -(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -lower alkylene-NRaRb, -lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -NRaCORb, -NRaCO-ORb, -NRaCO-NRbRc, -NRaCO-lower alkylene-NRbRc, -NRaCO-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), $-NRaSO_2Rb$, $-NRaSO_2$-NRbRc, $-NRaSO_2$-lower alkylene-NBbRc, $-NRaSO_2$-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -CONRaRb, $-SO_2NRaRb$, -COORa, $-SO_2Ra$, -CONRa-ORb, -OCORa, -ORa, -halogen, -CORa, $-NO_2$, -CN or -halogeno lower alkyl,

Ra, Rb and Rc: the same or different from one another, and each represents -H, -lower alkyl, -lower alkenyl, -lower alkynyl, -cycloalkyl, -cycloalkenyl, -aryl, -5- or 6-membered monocyclic heteroaryl or -lower alkylene-aryl,

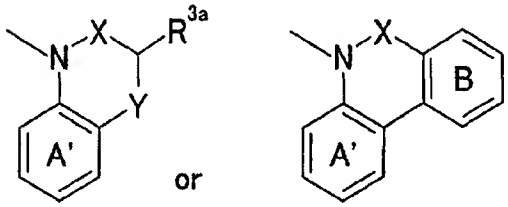
A: -aryl which may have one or more substituents,-heteroaryl which may have one or more substituents,-saturated carbon ring-condensed aryl which may have one or more substituents or

-saturated heterocyclic ring-condensed aryl which may have one or more substituents, wherein the saturated carbon ring-condensed aryl and saturated heterocyclic ring-condensed aryl bind to the adjacent N atom via C atom of the aromatic ring,

X: CO or SO_2,

R^3: -alkyl which may have one or more substituents,-alkenyl which may have one or more substituents, -alkynyl which may have one or more substituents, -cycloalkyl which may have one or more substituents, -cycloalkenyl which may have one or more substituents, -aryl which may have one or more substituents, -hetero ring which may have one or more substituents or

-NRaRb, or it may form a group represented by the following formula together with the adjacent group -N(-A)-X-,



Y: O, S, a bond or CH_2,

R^{3a}: -H, -cycloalkyl which may have one or more substituents,

-cycloalkenyl which may have one or more substituents,-aryl which may have one or more substituents or -hetero ring which may have one or more substituents, and

A' and B: the same or different from each other, and each represents benzene ring which may have one or more substituents).

2. The amide derivative or a salt thereof according to claim 1, wherein

R^1 and R^2 may be the same or different from each other and each represents -H, -lower alkyl, -lower alkenyl, -lower alkynyl, -NRaRb, -NRc-NRaRb,-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl), -NRc-C(=NH)-NRaRb, -NRaCORb, -NRaCO-ORb, -NRaCO-NRbRc, -NRaCO-lower alkylene-NRbRc or -NRaCO-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may be substituted with lower alkyl),

A is aryl which may have 1 to 5 substituents selected from a group D, heteroaryl which may have 1 to 5 substituents selected from the group D, saturated carbon ring-condensed aryl which may have 1 to 5 substituents selected from the group D or saturated heterocyclic ring-condensed aryl which may have 1 to 5 substituents selected from the group D, and R^3 is cycloalkyl which may have 1 to 5 substituents selected from the group D, cycloalkenyl which may have 1 to 5 substituents selected from the group D, aryl which may have 1 to 5 substituents selected from the group D, saturated carbon ring-condensed aryl which may have 1 to 5 substituents selected from the group D, saturated heterocyclic ring-condensed aryl which may have 1 to 5 substituents selected from the group D, heteroaryl which may have 1 to 5 substituents selected from the group D or 5- to 8-membered monocyclic saturated heterocyclic ring which may have 1 to 5 substituents selected from the group D,

wherein the group D comprises -(lower alkyl which may have 1 or 2 substituents selected from -ORa, -SRa, -CN, -COORa, -CONRaRb, -NRaRb and -(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl, -lower alkylene-COORa and -MRaRb), -lower alkenyl, -lower alkynyl,-halogeno lower alkyl, 5- or 6-membered monocyclic heteroaryl, -cycloalkyl, -cycloalkenyl, -aryl, -NRaRb, -NRc-NRaRb,-(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl, -lower alkylene-COORa and -NRaRb), -NRc-(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl,-lower alkylene-COORa and -NRaRb), -O-lower alkylene-NRaRb, -O-lower alkylene-(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl, -lower alkylene-COORa and-NRaRb), -O-lower alkylene-ORa, -O-lower alkyl-COORa,-COORa, -halogen, -CORa, $-NO_2$, -CN, -ORa, -O-(halogeno lower alkyl), -SRa, -SORa, $-SO_2Ra$, -CO-NRaRb, -CO-(nitrogen-containing saturated heterocyclic ring which may have one or more substituents selected from -lower alkyl,
-lower alkylene-COORa and -NRaRb), -NRa-CORb, $-SO_2NRaRb$ and =O(oxo).

3. The amide derivative or a salt thereof according to claim 1, wherein X is CO.

4. The amide derivative or a salt thereof according to claim 1, wherein R^1 is $-NH_2$ and R^2 is -H.

5. The amide derivative or a salt thereof according to claim 1, wherein it is selected from
N-({[4-(2-Aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(2,3-dihydro-1H-indol-6-yl)benzamide; N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(1,2,3,4-tetradihydroquinolin-6-yl)benzamide; N- ({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-fluorobenzamide; N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(1,3-benzodioxol-5-yl)-4-fluorobenzamide;N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-benzothiazol-5-yl-4-fluorobenzamide; N-({[4-(2-aminothiazol-4-yl) phenyl]carbamoyl}methyl)-N-benzothiazol-6-yl-4-fluorobenzamide; N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-indan-5-ylbenzamide; N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(3-hydroxyindan-5-yl)benzamide; N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(1H-indol-5-yl)benzamide; N-({[4-(2-aminothiazol-4-yl}phenyl]carbamoyl}methyl)-4-fluoro-N-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl)benzamide; N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-4-fluoro-N-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)benzamide; N-({[4-(2-aminothiazol-4-yl) phenyl]carbamoyl}methyl) -N-(1,2,3-benzothiadiazol-5-yl)-4-fluorobenzamide;N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-(4-methoxyphenyl) tetrahydro-2H-thiopyran-4-carboxamide 1,1-dioxide; N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl} methyl)-N-benzothiazol-5-yl-4-fluorocyclohex-3-enecarboxamide; N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl} methyl)-N-benzothiazol-5-yl-4,4-difluorocyclohexanecarboxamide; and N-({[4-(2-aminothiazol-4-yl)phenyl]carbamoyl}methyl)-N-indan-5-yltetrahydro-2H-thiopyran-4-carboxamide 1,1-dioxide.

6. A pharmaceutical composition which comprises the amide derivative or a salt thereof described in claim 1 and a pharmacologically acceptable carrier.

7. The pharmaceutical composition according to claim 6, wherein it is an anti-herpesvirus agent.

8. The pharmaceutical composition according to claim 7, wherein it is an anti-varicella zoster virus agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09790

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D277/40, 417/12, 417/14, A61K31/426, 31/427, 31/496, 31/4709, 31/4725, 31/428, 31/454, 31/5415, 31/536, 31/433, 31/4439, A61P31/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D277/40, 417/12, 417/14, A61K31/426, 31/427, 31/496, 31/4709, 31/4725, 31/428, 31/454, 31/5415, 31/536, 31/433, 31/4439

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1926-1996 Toroku Jitsuyo Shinan Koho 1994-2002
Kokai Jitsuyo Shinan Koho 1971-2002 Jitsuyo Shinan Toroku Koho 1996-2002

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6057451 A (Boehringer Ingelheim Pharmaceuticals Inc.), 02 May, 2000 (02.05.2000) (Family: none)	1-8
A	WO 00/29399 A(Boehringer Ingelheim (Canada), Ltd.), 25 May, 2000 (25.05.2000) (Family: none)	1-8
A	WO 99/42455 A (Tularik Inc.), 26 August, 1999 (26.08.1999) (Family: none)	1-8
A	WO 97/24343 A (Boehringer Ingelheim Pharmaceuticals Inc.) & JP 2000-502702 A & EP 871619 A & CN 1207094 A & BR 9612435 A & CA 2192433 A & ZA 9610850 A & NO 9802950 A	1-8
A	Simoneau Bruno, "Helicase-primase inhibitors as novel anti-HSV agents", Chimia, Vol.53, No.6, (1999), pages 297 to 298	1-8

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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January, 2002 (30.01.02)	12 February, 2002 (12.02.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)